ARCHIVES OF PATHOLOGY

VOLUME 17 MAY, 1934 NUMBER 5

CHEMOTROPISM OF LEUKOCYTES IN VITRO

ATTRACTION BY DRIED LEUKOCYTES, PARAFFIN, GLASS AND STAPHYLOCOCCUS ALBUS

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It is generally accepted that the accumulation of leukocytes in areas of inflammation is due to chemotropism (chemotaxis). These terms mean that the cell orients itself in a concentration gradient of the attracting substance and advances (supposing the reaction to be positive) toward regions of higher concentration.

Previous experiments on chemotropism of leukocytes fall into two groups. Experiments of the earlier group were designed to ascertain whether more cells collected about substances tested for chemotropic properties than about indifferent substances. Usually a number of capillary tubes containing different substances were inserted in the tissues of animals or in suspensions of leukocytes. If, at the end of the experiment, a tube was found to contain more leukocytes than the control tubes, the substance in that tube was considered to be positively chemotropic; if, on the contrary, there were fewer leukocytes than in the control tube, the substance was regarded as negatively chemotropic.[1]

These older experiments have been so fully reviewed by Wells [2] that they need not be discussed here in detail. They yielded much information, not all of which is reliable. Thus it has been shown by Pfoehl [3] and by Ruchlädew [4] that under certain conditions leukocytes may be carried passively into the tubes by convection currents, in which case erroneous conclusions might be drawn as to the chemotropic properties

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1. For a description of other methods, the reader is referred to the review by Philipsborn (Folia haemat. **43**:142, 1930).

2. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925.

3. Pfoehl, J.: Centralbl. f. Bakt. **24**:343, 1898.

4. Ruchlädew, N.: Ztschr. f. Biol. **54**:533, 1910.

of a given substance. (A further critique of this method is to be found in an article by Marchand.[5])

In the second and more recent group of experiments a different criterion was used, namely, whether cells moved toward or away from the substance to be tested or whether they moved indifferently. These observations were made directly with the microscope.

Thus Commandon observed and recorded cinematographically the attraction of leukocytes by certain parasites in the blood [6] and by grains of starch.[7] Fenn [8] observed that leukocytes were attracted by particles of manganese dioxide but not by quartz.

Jochims [9] studied the reactions of leukocytes to solutions diffusing through a collodion membrane and found them to react positively to certain solutions and negatively to others. Schade and Mayr [10] made serial photographic records of cells moving toward dried drops of pus and drops of paraffin containing turpentine. With the same method, Schulz observed that leukocytes were attracted by certain bacteria and their products,[11] and Rosegger [12] reported the attraction in vitro of horse eosinophils by bits of parasitic worms.

Such direct observations on the direction of locomotion possess a great advantage over the older capillary tube method in that passive transportation of leukocytes (by convection currents) can be excluded; it may actually be seen whether the cell is moving by its own ameboid motion. However, it seems to us that such observations would gain in dependability and significance if the factor of random locomotion were controlled. The fact that a cell moves toward an object does not inevitably mean that the cell is attracted by it. We have observed leukocytes travel as far as 250 microns in a fairly straight line even in the absence of any known source of attraction.

Therefore, in the experiments reported here we sought to control the factor of random locomotion. This was done by counting the number of polymorphonuclear leukocytes that in unit time made contact with the attracting body; this figure was compared with the number of cells that made contact with an imaginary body of the same size and shape located in another part of the preparation.

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5. Marchand, F., in Krehl, L., and Marchand, F.: Handbuch der allgemeinen Pathologie, Leipzig, S. Hirzel, 1924, vol. 4, pt. 1, p. 336.

6. Commandon, J.: Compt. rend. Soc. de biol. **80**:314, 1917.

7. Commandon, J.: Compt. rend. Soc. de biol. **82**:1171, 1919.

8. Fenn, W. O.: J. Gen. Physiol. **5**:311, 1923.

9. Jochims, J.: Arch. f. d. ges. Physiol. **216**:611, 1927.

10. Schade, H., and Mayr, K.: Krankheitsforschung **8**:354, 1930.

11. Schulz, E.: Ztschr. f. d. ges. exper. Med. **84**:609, 1932.

12. Rosegger, H.: Ztschr. f. d. ges. exper. Med. **85**:712, 1932.

By this method we sought to answer the questions of whether cells are attracted by certain bodies or only accidentally make contact with them, and whether the accumulation of leukocytes about certain bodies is due to chemotropism or to the trapping [13] of cells which have been moving at random.

EXPERIMENTS

In the first series of experiments the attracting body consisted of a mass of dead (dried) leukocytes. This material was selected because in earlier (unpublished) work we had repeatedly observed that leukocytes frequently move toward, and make contact with, dead or immobile leukocytes accidentally present in the preparation. It seemed likely, therefore, that a clump of immobile leukocytes would strongly attract moving ones.

The attractive power of dead cells was tested by a modification of a simple method previously used for measuring the rate of locomotion of leukocytes.[14] Human blood was centrifugated, and from the buffy coat a minute drop of leukocytes was transferred to an ordinary glass slide. It was allowed to dry for several hours, and a flat body was obtained, about 400 microns in diameter. A drop of fresh blood from the same person was placed on a coverslip, lowered on the slide and allowed to spread in such a way that the clump of dried cells lay in the middle of the preparation. After the preparation was sealed with petrolatum, it was placed in the warm box at 37 C. We waited half an hour to allow the cells to develop normal locomotion. The clump of dried leukocytes was brought into the microscopic field and placed at the periphery. The image of the field was projected onto a piece of paper by a drawing ocular, as previously described,[14] and the position of each leukocyte was recorded at intervals of approximately one minute. In half an hour a record was obtained such as is shown in figure 1. Of the 9 cells that came into the field, 5 made contact with the mass of dried leukocytes, 3 moved out of the field and the remaining cell moved at random in the field. (Part of the path of this cell [*2*] has been omitted to avoid confusion.) It will further be observed that of the cells that made contact with the dried leukocytes, *1, 6* and *7* did so only after previous random movement. The impression gained from this experiment is that the leukocytes were attracted by the dried cells, but only weakly and from no great distance.

As a control experiment we determined the number of chance contacts made by cells wandering at random. For this purpose we drew on a fresh sheet of paper an imaginary attracting body of the same size and shape as the real one, and a field picked at random was projected

13. A foreign body acts as a trap; cells coming in contact with it remain in the interface between the foreign body and the blood for a shorter or a longer time.

14. McCutcheon, M.: Am. J. Physiol. **69**:279, 1924.

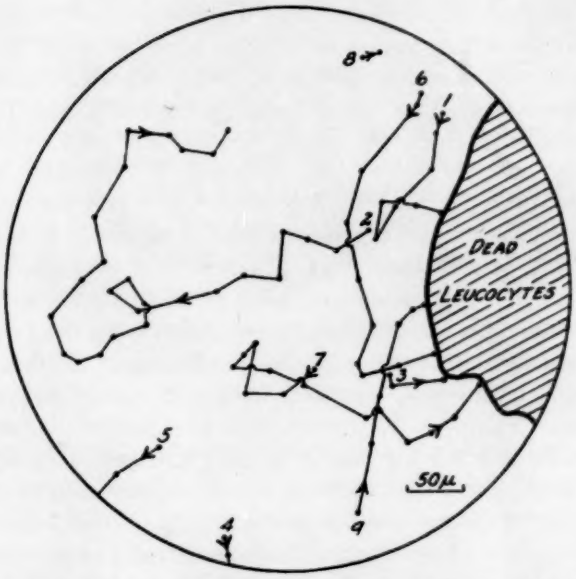

Fig. 1.—Camera lucida record of the paths of the 9 leukocytes that were seen in half an hour in a field containing a mass of dried leukocytes (shaded area). The dots represent the position of the leukocytes at intervals of approximately one minute. It is seen that during this time 5 of the cells (*1, 3, 6, 7* and *9*) made contact with the attracting body while the remaining 4 did not.

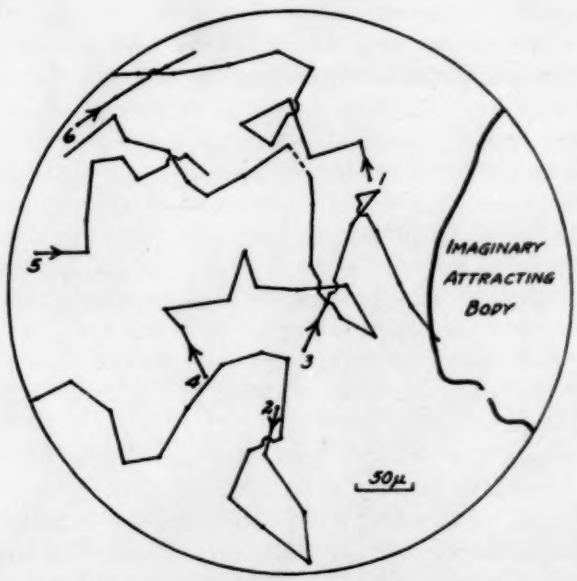

Fig. 2.—The attracting body is imaginary. Only 1 cell (*3*) made contact with it in half an hour; the locomotion of the cells was at random.

on it. The paths of leukocytes were recorded for half an hour, as shown in figure 2. It is seen that the paths are at random. (In several instances the complete path is not shown, in order to avoid confusion.)

Since it was found that cells coming into contact with the mass of dried leukocytes were usually trapped by it, cells "making contact" with the imaginary attracting body were treated as if trapped by it, and their further path disregarded. Thus, no cells were counted as making more than one contact with either the real or the imaginary attracting body. Any leukocytes that happened to be within the imaginary body were not counted. This procedure has the same effect as putting in the control field an actual object that exerted no chemotropic effect but that could trap leukocytes.[15]

In figure 2 it is seen that during the half hour 1 cell "came in contact" with the imaginary attracting body, as contrasted with 5 cells which made contact with the real attracting body. The procedure was then repeated both with the real and with the imaginary attracting body, so that at the end of the experiment the number of cells that had made contact with each in one hour was known. In the present experiment these numbers were respectively 6 and 1.

It is, however, not possible to draw any significant conclusion from one such experiment, since the number of cells is small and the difference in number of contacts might be obtained by chance. Therefore, the experiment was repeated a number of times.

In table 1 are summarized the results of ten such experiments. It is seen that in each experiment more cells made contact with the real than with the imaginary attracting body. The respective numbers for the entire series are 100 and 20, that is, five times as many cells made contact with the dried leukocytes as with the imaginary body in the control. In all, 202 cells were observed in the fields containing the real attracting body, of which 100, or 50 per cent, made contact. In the control fields, 170 cells were observed, of which 20, or 12 per cent, made contact.[16]

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15. The validity of this method depends on the fact that the field in the control experiment is chosen at random and a sufficiently large number of experiments made.

16. If correction were made for the difference in the number of cells in those fields containing dried leukocytes and in the control fields, the ratio of contacts in the two cases would be about 4:1 instead of 5:1 as given. But in later experiments, counts of the number of cells in different areas, made immediately after the preparation was placed in the warm box and before any migration occurred, showed the same number of cells near the attracting body as in distant fields. It therefore seems likely that in the present experiments the reason for the unequal distribution of cells was that more cells wandered from adjacent regions into the area containing the dried leukocytes than into the area containing the imaginary attracting body. In this case, therefore, no correction in the ratio is necessary.

We conclude from these results that leukocytes were definitely attracted by dried cells.

But before any significance can be attached to this result, the question must be answered as to whether the attraction was due to the dried cells in particular or whether any other solid material would have attracted the leukocytes as well.

Accordingly, in another series of experiments, instead of dried leukocytes we used such relatively inert and insoluble material as a

TABLE 1.—*Results of First Series of Experiments* *

Experiment	Number of Cells Making Contact with	
	Mass of Dried Leukocytes	Imaginary Body
1	6	1
2	9	2
3	11	4
4	18	1
5	4	0
6	13	3
7	5	2
8	11	2
9	13	2
10	10	3
Total hits	100	20
Cells making contact per hour	10	2

* In each experiment the number of cells was counted that made contact with a mass of dried leukocytes in one hour (in experiment 3, seventy minutes), and compared with the number making contact with an imaginary body of the same size and shape in the same period of time. On the average, five times as many cells made contact with the dried leukocytes as with the imaginary body.

minute drop of paraffin wax, a bit of glass coverslip or a fine glass thread. Records were made showing the number of cells making contact with such an inert body and with an imaginary body of the same size.

In table 2 are summarized the results of twelve such experiments. Since not enough experiments have been made with different bodies to distinguish between them, they have been grouped together. It is seen that an average number of 6.6 cells per hour made contact with the actual body and 2.4 cells per hour with the imaginary body. This difference indicates that there is still an attractive force, though not as great as was exerted by the dried leukocytes.

Thus we have the result that comparatively insoluble substances sometimes definitely attract leukocytes. Similar observations have been made by others. Marchand [5] reported that leukocytes are attracted by fibrin; Philipsborn [1] saw them attracted by threads. Metchnikoff [17] found that amebocytes and leukocytes of various invertebrates collect around supposedly inert foreign bodies. Shaeffer [18] reported that amebas

17. Metchnikoff, E.: Comparative Pathology of Inflammation, London, Kegan Paul, Trench, Trübner & Co., 1893.

18. Shaeffer, A. A.: Biol. Bull. **31**:303, 1916

TABLE 2.—*Results of Second Series of Experiments* *

	Number of Cells Making Contact with	
	Paraffin	Imaginary Body
	4	0
	1	3
	1	2
	10	1
	12	4
	4	3
	10	2
	Glass	
	0	2
	11	0
	17	9
	2	1
	Fiber	
	7	2
Total hits.....	79	29
Cells making contact per hour	6.6	2.4

* In each of twelve experiments, the number of cells making contact with a foreign body in one hour is compared with the number making contact with an imaginary body of the same size and shape in the same period of time. Combining the experiments, the ratio is about 2.7 : 1.

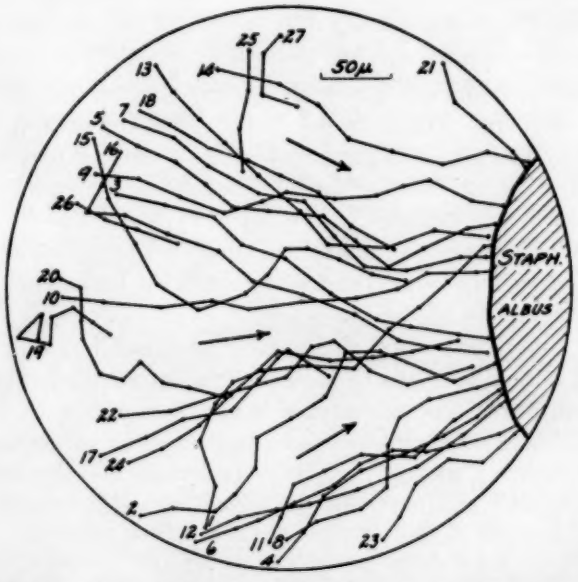

Fig. 3.—When the attracting body (shaded area) was composed of staphylococci, all the leukocytes advanced in nearly a straight line toward it. In half an hour 17 cells made contact.

thrust out pseudopods toward particles of glass and carbon from 60 to 100 microns distant.

The mechanism of such attraction is not known. In our experiments the following possibilities are suggested: 1. In some of the experiments the bodies may have been contaminated with a chemotropic substance. 2. Leukocytes making chance contact with the bodies were trapped and may have given off chemotropic substances. 3. The observation by Schulz,[11] that charcoal may take up a chemotropic substance from the medium and then attract cells, suggests the possibility of a similar mechanism in our experiments. 4. The bodies may have been sufficiently soluble to be themselves chemotropic.

The attractive force exerted by all the substances studied—glass and paraffin as well as dried leukocytes—seems to be quite definite, though certainly weak. For comparison with a strong chemotropic source, we present figure 3, in which the attracting body was a clump of Staphylococcus albus. In this figure it is seen that many leukocytes have entered the field and are all proceeding in more or less straight lines toward the attracting body. This is a typical example of the strong attraction which we found, in every experiment, to be exerted by Staphylococcus albus and a variety of other micro-organisms.[19] In seven experiments with Staphylococcus albus, the average number of cells making contact per hour was 22. By comparison with these micro-organisms, the attracting powers of dried leukocytes, paraffin and glass are seen to be weak.

SUMMARY

A method is described for studying the chemotropic response of leukocytes in vitro. The number of cells making contact with the attracting body in an hour is compared with the number making contact with an imaginary body of the same size placed at random in the field of leukocytes.

Dried leukocytes were found to attract polymorphonuclears weakly; about five times as many cells moved to the dried leukocytes as moved to an imaginary body of the same size.

Relatively inert substances like paraffin wax and bits of glass were also found by these methods to have a slight attraction for leukocytes. Possible mechanisms for such attraction are discussed.

Different kinds of micro-organisms were tested and all were found to attract leukocytes strongly. When Staphylococcus albus was used, all polymorphonuclears in the neighborhood moved to the bacteria in practically a straight line.

19. The results of experiments with micro-organisms will be reported later.

EFFECTS OF OXYACIDS AND HYDROXYACIDS ON PROTEIN SWELLING

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The notion that the action of an acid on the swelling of a protein colloid is the product of the hydrogen ions yielded by that acid when dissolved in water has been a dead issue to many workers in biology since early days,[1] yet its continuance into the literature of today by the followers of such workers as S. P. L. Sörensen,[2] Leonor Michaelis,[3] Henry R. Procter [4] and Jacques Loeb [5] justifies any renewed attack on the problem. The experiments detailed here on the effects of different acids on the swelling and "solution" of a highly purified globulin (a commercial Harris casein with 0.59 per cent of ash) may again be cited as quantitative evidence of the failure to find any relation between such effects on protein and the "strength" of the acids employed. They were not made, however, with this purpose first in mind but rather to get at an understanding of what might be the difference in the physiologic action of any simple acid as this was changed to the corresponding hydroxyacid or oxyacid. Thus the normal butyric acid of the fats consumed by man has a pathologic sister in the hydroxybutyric acid that appears in diabetes; propionic acid (from fat or protein), in the lactic acid discoverable in nonoxygenated muscle or in the body fluids in disease of the heart. In the plant world, on the other hand, acetic acid has a chemical teammate in the hydroxyacetic acid of unripe fruits, and succinic acid, in hydroxysuccinic (malic) and dihydroxysuccinic (tartaric) acid.

From the Eichberg Laboratory of Physiology, the University of Cincinnati.

1. Fischer, Martin H.: Am. J. Physiol. **20**:332, 1907; Œdema, New York, John Wiley & Sons, 1910, pp. 31 and 33.

2. Sörensen, S. P. L.: Letter to the editor, Kolloid Ztschr. **40**:163, 1926.

3. Michaelis, L., in Alexander, J.: Colloid Chemistry, New York, Chemical Catalog Company, Inc., 1926, vol. 1, p. 498.

4. Procter, Henry R.: Kolloidchem. Beihefte **2**:270, 1911.

5. Loeb, Jacques: Contributions to Medical and Biological Research, Dedicated to Osler, New York, Paul B. Hoeber, Inc., 1919, vol. 2, p. 861. Bogue, R. H.: Theory and Application of Colloidal Behavior, New York, McGraw-Hill Book Company, Inc., 1924, vol. 1, p. 23.

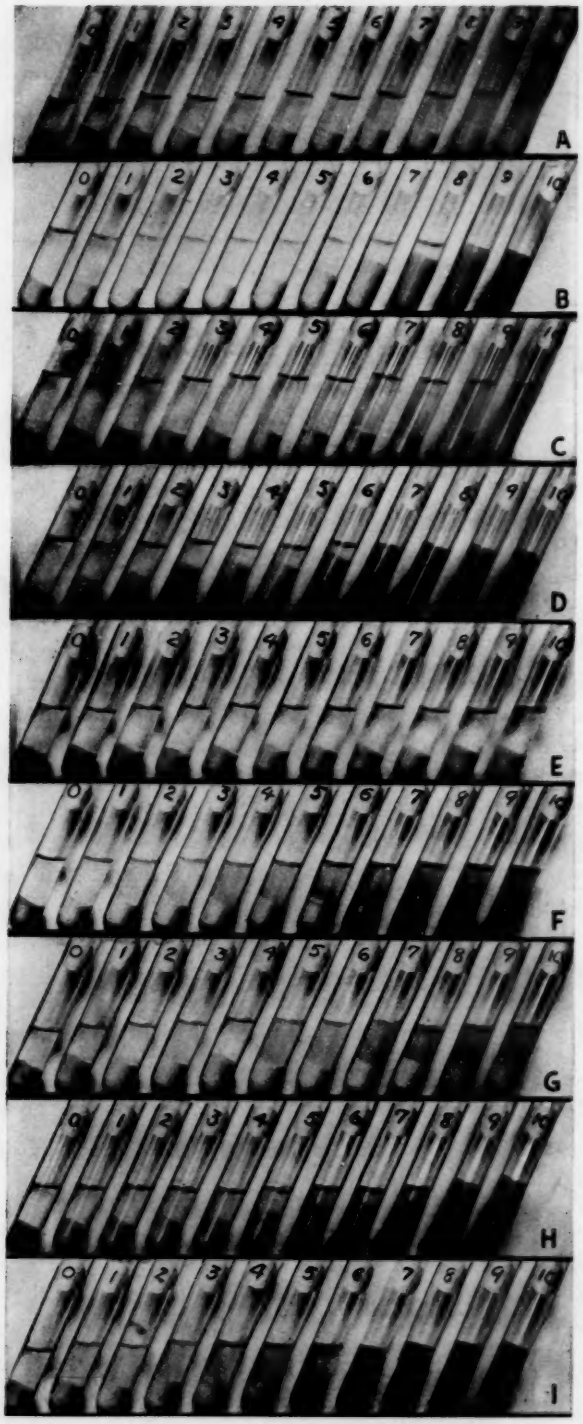

Fig. 1.—The several series of tubes show the effects of equimolar concentrations of different acids and hydroxyacids on casein. The successive series illustrate the effects of acetic, hydroxyacetic (glycolic), propionic, hydroxypropionic (lactic), butyric, hydroxybutyric, succinic, hydroxysuccinic (malic) and dihydroxysuccinic (tartaric) acids.

EXPERIMENTAL DATA

Experiments showed that the hydroxylation of an acid generally increases the activity of that acid in producing the swelling and the "solution" of a protein (casein). Figure 1 *A* to *I* illustrates the effect better than many words. The tubes carry in all cases a unit weight of casein (0.625 Gm.) in a unit volume of "solvent" (5 cc.). The tubes marked 0 are controls, containing casein and water only. The others, numbered from 1 to 10, show the effects of increasing concentra-

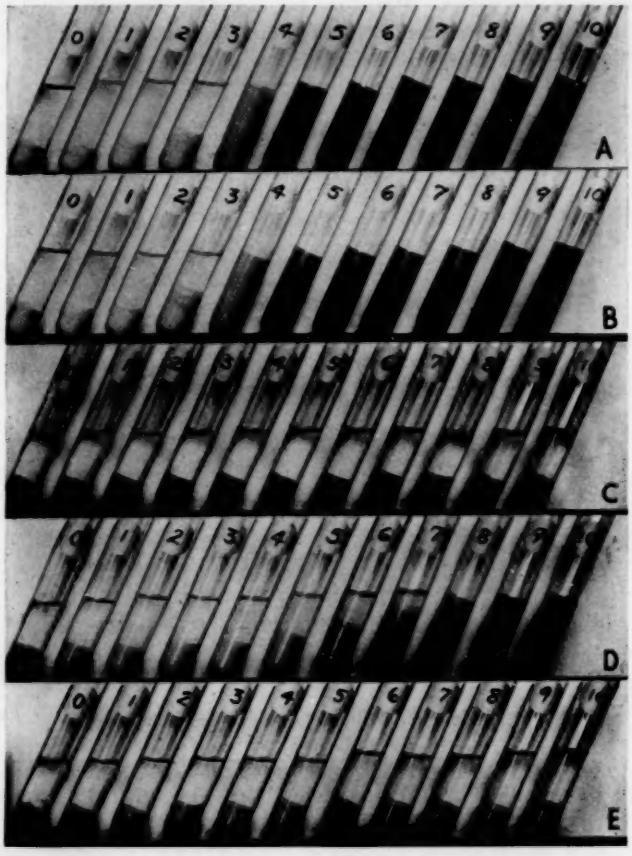

Fig. 2.—Effects of equimolar concentrations of several oxyacids on casein. The successive series illustrate the effects of phosphorous and phosphoric acids, and of hydrosulphurous, sulphurous and sulphuric acids.

tions of acid (in decimal increments from hundredth molar to ten-hundredths molar). Within this range of concentration acetic acid is seen to bring about almost no swelling (fig. 1 *A*). Hydroxyacetic acid, on the other hand, is so effective that increase in the height of the casein column is noticeable in tube 5 (fig. 1 *B*), while from tube 9 on the contents have swollen into solid gels. The effects of hydroxypropionic (lactic) as opposed to propionic acid may be seen by comparing figure 1 *D* with figure 1 *C;* that of hydroxybutyric against butyric acid,

by comparing figure 1 *F* with figure 1 *E*. In the series on succinic acid the barely appreciable swelling produced by the mother substance (fig. 1 *G*) becomes marked in hydroxysuccinic (malic) acid (fig. 1 *H*) and is further increased in the dihydroxyacid (tartaric) acid, as indicated by the shift of the swollen and gelled columns of casein toward the left in figure 1 *I*.

The effects of some oxyacids as opposed to the pure acids are illustrated in figure 2 *A* to *E*. Phosphorous acid (fig. 2 *A*) proves quite as active as phosphoric acid (fig. 2 *B*), both relatively and absolutely. Figure 2 *C* to *E* compares a series of the acids of sulphur. Hydrogen sulphide (fig. 2 *C*) is practically without effect in the concentrations here detailed. Sulphurous acid (fig. 2 *D*) produces a large effect, but this recedes practically to the level of no effect when sulphuric acid (fig. 2 *E*) is used.

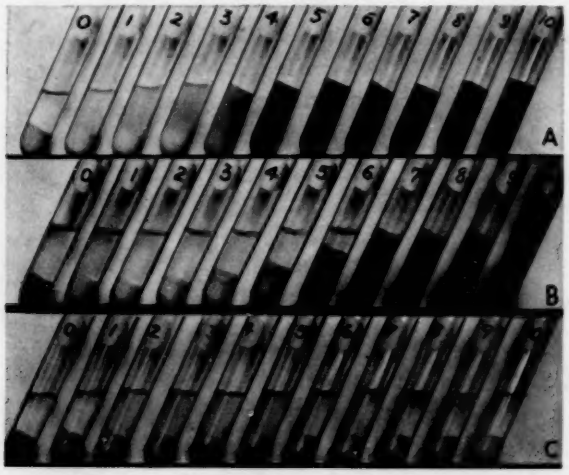

Fig. 3.—Successive series showing the effects of equimolar concentrations of hydrochloric, chloric and perchloric acids.

Figure 3 *A* to *C* compares the action of hydrochloric acid with two of the oxyacids of chlorine. Figure 3 *A* shows hydrochloric acid (of about the same p_H as the ineffective sulphuric acid of figure 2 *E*) to bring about an appreciable swelling in tube 3, after which its activity is so great that the contents of the remaining tubes set in solid gels. Chloric acid (fig. 3 *B*) though much "weaker" is not far behind, while perchloric acid (fig. 3 *C*) leaves the casein practically unaffected so far as its swelling and solution are concerned in the concentrations here employed.

CONCLUSIONS

Quantitative studies are detailed showing the effects of different acids on the swelling and "solution" of a highly purified casein. The action of the acids in no fashion parallels their electrolytic dissociation but each acts specifically. On comparing certain acids with their hydroxyacids it was found that the latter were uniformly more active. The effects of the oxyacids as contrasted with their mother acids cannot

be so easily compared. Little difference exists between the action of phosphorous and phosphoric acids; the acids of sulphur show greatest activity in a midzone of oxidation; of the acids of chlorine, hydrochloric is most active, with the oxyacids growing progressively weaker in this regard as the oxygen element is increased.

AMYLOIDOSIS OF THE BONE MARROW

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The bone marrow is not a frequent site of amyloid deposits. When present in the bone marrow, amyloid is usually found in three forms, namely, isolated infiltrations of the vessels of the marrow in generalized amyloidosis, massive accumulations in the form of tumors, and deposits within preexisting blastomas or otherwise diseased bones.

In generalized amyloidosis the bone marrow is generally spared. Ponfick,[1] who first thoroughly investigated the bones for changes in amyloid disease, found but few instances of infiltration of the small and medium-sized arteries in the marrow. Eberth,[2] Wichmann [3] and others had the same experience. Askanazy,[4] who also methodically examined the bone marrow in cases of generalized amyloidosis, likewise reported only occasional instances of vascular infiltration.

A second form in which amyloid is found in the marrow is that of massive accumulations in the skeleton. These have been designated amyloid tumors of the bone, to indicate the tumor-like character of the amyloid deposit; they are not to be considered true blastomas of the bones. In these instances the amyloid deposits are more or less sharply localized in one or several sites in the skeleton. The uninvolved portion of the affected bone, as well as the remaining bones, is not infiltrated. The amyloid tumors of the bone have been described as occurring either alone or combined with amyloid deposits in the internal organs.

The third form in which amyloid is found in the bone marrow is that of a deposition of the amyloid within blastomas or otherwise diseased bones. In such instances the amyloid deposits are considered secondary to the underlying blastomas or chronic diseases, in contradistinction to the amyloid tumors of the bone which are considered primary or idiopathic. While the amyloid may be limited to the diseased bone, it is not infrequently found in the internal organs as well. The unaffected portion of the diseased bones and the remaining bones of the body are not infiltrated. The three forms of amyloid deposits in the bone marrow will be discussed later.

From the laboratories of the Mount Sinai Hospital.

1. Ponfick, E.: Virchows Arch. f. path. Anat. **56**:534, 1872.
2. Eberth, C. J.: Virchows Arch. f. path. Anat. **80**:138, 1880.
3. Wichmann, G.: Beitr. z. path. Anat. u. z. allg. Path. **13**:487, 1893.
4. Askanazy, M., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, p. 835.

A survey of the literature has failed to disclose a description of diffuse amyloid infiltration of the bone marrow, that is, a diffuse involvement of the marrow comparable to that seen in the spleen or other hematopoietic organs. The following case represents such a condition.

REPORT OF A CASE

History.—A white man, aged 44, was admitted to the medical service of Dr. George Baehr at the Mount Sinai Hospital on March 29, 1928, complaining of pruritus, postprandial pyrosis, vague muscular pains and weakness. An examination revealed hepatomegaly, albuminuria, hypercholesteremia and a rapid disappearance of congo red injected into the blood stream. A diagnosis of amyloidosis, amyloid nephrosis, hypercholesteremia and lipoid histiocytosis was made. Frequent observation showed persistent albuminuria and hypercholesteremia, the cholesterol rising as high as 0.625 Gm. per hundred cubic centimeters of blood. Roentgen ray examination of the bones revealed no changes. About two and one-half years after the first admission signs of renal insufficiency and hypertension supervened; these were attributed to incipient renal contraction secondary to amyloid nephrosis. At this time further roentgen studies revealed a collapse of the bodies of the ninth thoracic and first lumbar vertebrae. Biopsy showed a hyperplastic lymph node with lipoid in some of the cells; the lipoid was not doubly refractile and did not stain with sudan. Because of the changes in the lymph node and the hypercholesteremia a diagnosis of lipoid infiltration of the bones was made. Hypertension persisted to the end. The renal insufficiency and vertebral lesions progressed until the patient died on March 10, 1931, of azotemia and pulmonary edema.

Autopsy.—An autopsy was done on March 10, 1931, four hours after death, by Dr. S. Otani and Dr. A. Schifrin.

The body was somewhat emaciated; no jaundice, edema, petechiae or scars were noted. The lungs were edematous. The heart showed a moderate hypertrophy of the left ventricle. The liver was enlarged to about two and one-half times its normal size and weighed 3,720 Gm. Section revealed a dull, waxy, reddish-brown surface with indistinct lobular structure. (The reddish tint was ascribed to the retention of congo red administered during life.) The spleen was firm and weighed 140 Gm. The cut surface was pinkish red; the malpighian bodies were not distinctly visible. The pancreas and suprarenal glands appeared to be unaltered. The right kidney weighed 120 Gm. and the left 110 Gm. The surfaces appeared smooth; however, on examination with a hand lens fine granulation was detected. The cut surface was dull and waxy; the corticomedullary relationship was normal. The glomeruli were seen distinctly as small, bright red dots. Pinkish striations were seen coursing from the cortex to the medulla. (The glomeruli and tubules stained intravitally with congo red.) The thyroid was firm and fleshy. There were healed erosions of the stomach and duodenum. Nowhere in the body were the lymph nodes enlarged. They were, in general, of the size of a pea, soft and on section characteristically grayish red.

Vertebrae: The anterior half of the bodies of the vertebrae from the eighth thoracic to the second lumbar was removed (fig. 1). The vertebral bodies were easily cut with a dull knife, except for the denser cortical portions just beneath the intervertebral disks. Instead of the network of spongy bone and red marrow usually seen, the cut surface was homogeneous, mahogany-colored, dull and waxy, and the framework of the spongy bone was not discernible. The marrow was of

putty-like consistency and, together with friable particles of spongy bone, could be readily scooped up on the back of a knife. Along the margins, especially the lateral, the cortical bone was less firm than normal and friable. The bodies of the ninth thoracic and first lumbar vertebrae were collapsed and deformed, resembling the vertebrae of a fish, and were only about one-fourth their original size. The margins of the collapsed vertebrae bulged laterally, while the surfaces adjoining the intervertebral disks, particularly the central portions beneath the expanded spongiosa of the disks, were depressed. Spicules of bone projected from the

Fig. 1.—Section of the anterior half of the bodies of the eighth, ninth, tenth, eleventh and twelfth thoracic and first and second lumbar vertebrae. Note the collapsed ninth thoracic and first lumbar vertebrae, with the expansion of the adjoining intervertebral disks. The marrow appears homogeneous; the framework of the spongy bone cannot be discerned.

depressed cortex into the pultaceous marrow. Above and below the collapsed vertebrae the intervertebral disks were elliptically expanded. There was no evidence of invasion of the surrounding muscle and connective tissue by tumor or amyloid.

Other Bones: The femoral marrow was reddish yellow, fatty and diffluent. The ilia possessed a dense, firm cortex, and the marrow was mahogany-colored, homogeneous and pultaceous; the spongy framework of the bone was not discernible. The ribs fractured readily, and the marrow resembled that of the vertebrae and ilia.

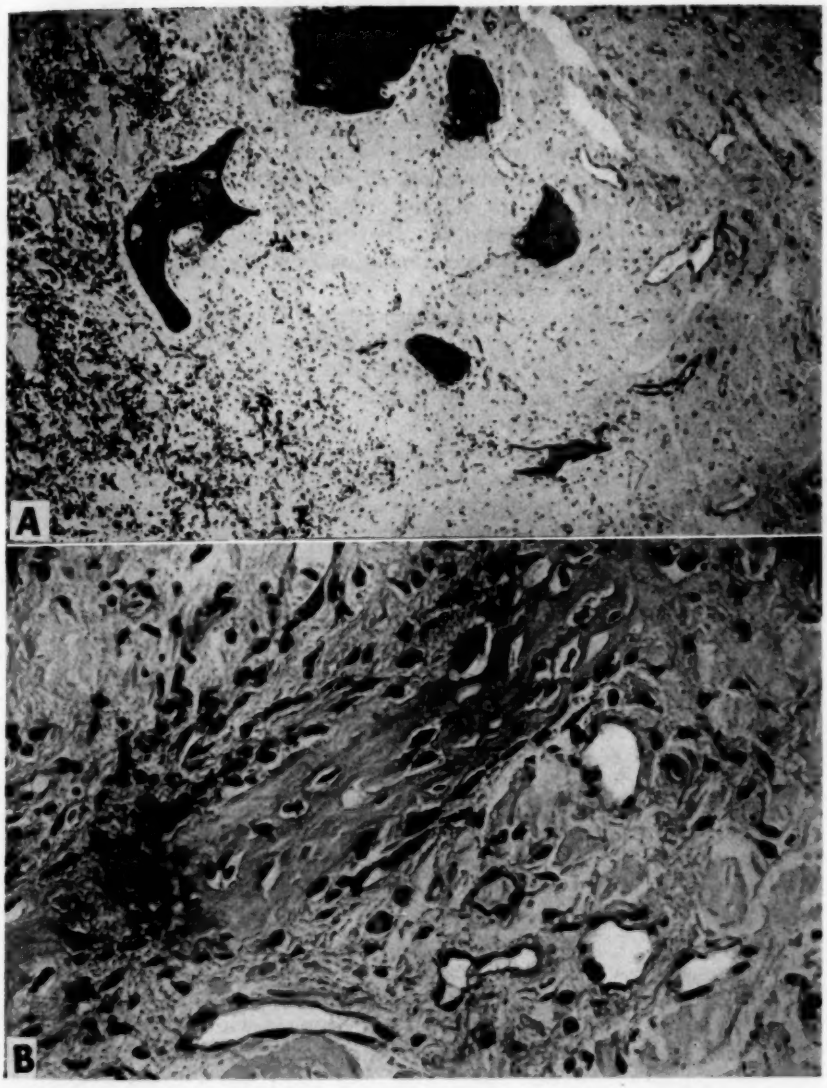

Fig. 2.—*A*, low power magnification of a vertebra, showing a central mass of amyloid and remnants of bony trabeculae. In the upper left corner the amyloid masses are seen infiltrated between the marrow cells, dividing them into islands. Note the regularity of the margin of the trabecula along which remnants of hematopoietic cells are still present. Hematoxylin and eosin. *B*, higher power magnification of a vertebra showing dilated sinusoids and fragment of a bony trabecula surrounded by amyloid. Large osteoclasts are seen along the margins of the trabecula; a multinucleated giant cell is present in a lacunar indentation. A small area of osteoid tissue can be seen just above the trabecula. Hematoxylin and eosin.

Because of permission for limited autopsy only, the brain and skull were not examined.

Microscopic Examination.—Vertebrae: Many sections were taken from the thoracic and lumbar vertebrae. Instead of the broad anastomosing lamellae there was a marked irregularity of the bony trabeculae, in both size and shape, and a replacement of the marrow by a mass of cell-free tissue. The cell-free tissue consisted of a structureless, homogeneous mass, generally taking a faint pink stain with eosin. Focal areas, in the vicinity of blood vessels, stained more deeply pink. The cell-free tissue was identified as amyloid by its staining reactions, particularly with the aniline dyes. Certain peculiarities of the amyloid staining reactions will be discussed in detail later.

The most marked infiltration of the bone marrow by amyloid, together with the most severe alteration of the spongy bone, was seen in the central areas of the vertebrae (fig. 2*A*). At those sites the amyloid was often arranged in more or less irregular islands demarcated by remnants of marrow cells. In the areas devoid of marrow cells the amyloid lay directly against the bony trabeculae. Numerous thin-walled, widely dilated sinusoids were present throughout. The amyloid in the walls of the sinusoids stained more intensely than the surrounding amyloid. The lumens of the arteries, small and large, were patent. The media of the arteries was homogeneous in appearance and stained positively for amyloid. Small, coarse clumps of amyloid were present in the adventitia and periadventitial tissues. The cells between the islands of amyloid were chiefly surviving hematopoietic cells, although occasional reticular cells and macrophages were seen.

Toward the cortex the surviving hematopoietic tissue was more abundant. Nevertheless, even at those sites the amyloid was seen to have infiltrated between the cells and divided them into irregular islands (fig. 2*A*). Directly beneath the cortex the marrow cells showed, as a rule, less amyloid infiltration; they were in normal relation to the bony trabeculae. The marrow cells showed a normal ratio of immature and mature myeloid and erythropoietic elements. There was no apparent change in the number of megakaryocytes; the reticular cells were discernible between the marrow cells. Aside from the occasional macrophages noted in the central areas of the vertebrae, no other adventitious cellular elements were noted.

The alteration of the bony trabeculae was most marked in the center of the vertebrae, where only small fragments of the spongy bone were seen. The margins of these remnants of bone were irregular and showed many lacunar indentations; the endosteum was disrupted. Closely applied to the irregular edges of the bone there was usually a row of large cells with abundant cytoplasm and a large nucleus that stained deeply blue with hematoxylin. In addition many multinucleated giant cells with tonguelike processes were seen along the margins of the bone and in the lacunar indentations (fig. 2*B*). Besides lacunar absorption many of the bony trabeculae showed advanced decalcification and resorption. There were scattered areas of osteoid tissue surrounding small fragments of bone (fig. 2*B*). Beneath the cortex the trabeculae of bone were generally large, broad and of regular outline; often, however, several showed early lacunar absorption or decalcification. The cortical bone was unaltered.

The destruction of the bony trabeculae was more or less sharply limited to those segments that were intimately surrounded by amyloid. No such alteration was noted where the bone was surrounded by marrow cells. In none of the sections were there evidences of the formation of new bone. There was no evidence of inflammation or tumor, in the bone, bone marrow or surrounding fibrous tissue.

The amyloid in the vertebrae did not stain with iodine or iodine and sulphuric acid. The amyloid in the media of the large and medium-sized arteries stained deeply red with congo red; the main mass of amyloid did not stain with this dye. With the aniline dyes a varied picture was observed. All the aniline dyes employed stained the amyloid equally well; cresyl violet, however, gave the most distinct picture. While the major portion of the amyloid in the center of the vertebrae stained a faint metachromatic pink, the scattered coarse clumps seen in the vicinity of the vessels and the amyloid in the media of the arterioles and walls of the sinusoids stained deeply violet. Between these two intensities there were many gradations in the metachromasia. Toward the periphery of the vertebrae and in

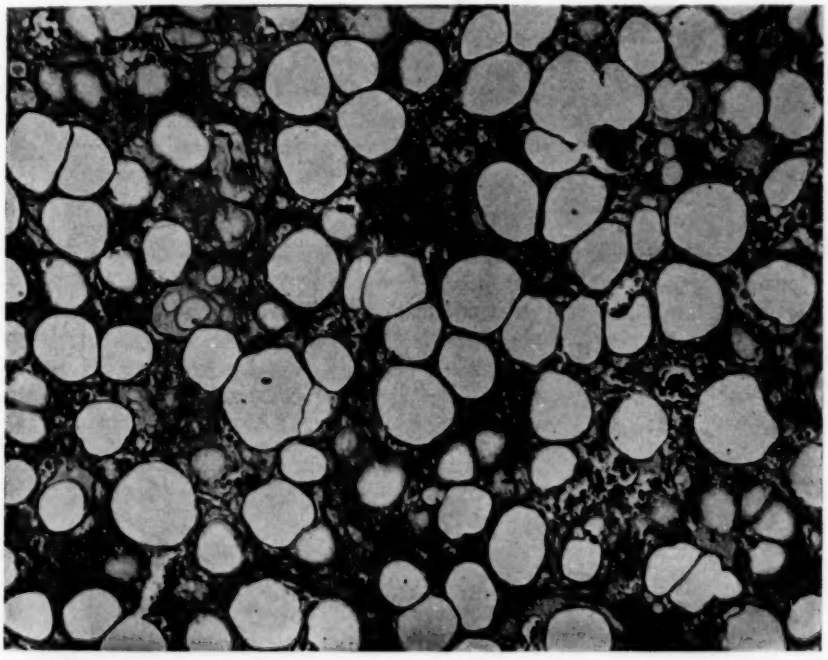

Fig. 3.—Fatty marrow of the femur showing diffuse amyloid infiltration between fat cells. Low power magnification. Hematoxylin and eosin.

between the large islands of hematopoietic tissue the amyloid stained more intensely, approaching a metachromatic purple. No amyloid was seen in the giant cells in the lacunae of the bone or in the macrophages.

Marrow of the Femur: There was a diffuse infiltration of amyloid in the spaces between the fat cells (fig. 3), and although a varying degree of compression of the fat cells was evident, no atrophy was noted. The hematopoietic elements showed the normal ratio of mature and immature cells. The distribution of the amyloid in the vessels, the alteration of the bony trabeculae and the staining of the amyloid were identical with the observations on the vertebrae.

Kidneys: The glomeruli were increased in size and markedly infiltrated with amyloid. The glomerular capillaries were seen with difficulty; they contained little blood. There was a marked increase of interstitial tissue, within which many

atrophic and collapsed tubules were seen. The remaining tubules were dilated; the epithelium showed marked granular degeneration, and the basement membrane was thickened by an infiltration of amyloid. The media of the small and medium-sized vessels showed marked amyloid deposition; the larger vessels were free. The lumens of all the vessels were patent. Some of the interlobular arteries showed a moderate degree of intimal proliferation and reduplication of the elastica; although carefully looked for, this change was not often observed.

Lymph Nodes: The architecture of the nodes was unaltered. The cortical follicles and lymphatic cords were depleted of cells. The sinuses were dilated and contained many macrophages and small lymphocytes. There was no evidence of lipoid-containing cells. Amyloid was not present.

Pancreas: The interlobular and intralobular connective tissue was increased and diffusely infiltrated with amyloid, which involved also the media of the small vessels. The basement membrane of the acinar cells and the islets of Langerhans were not infiltrated. The large vessels and ducts were free from amyloid.

Other Organs: The liver, spleen, thyroid, suprarenal glands and the mucosa of the stomach showed the characteristic picture of diffuse amyloid infiltration with involvement of the small and medium-sized vessels. The other organs exhibited no significant change.

In none of the tissue sections was it possible to stain the amyloid with iodine or iodine and sulphuric acid. Except for the variations noted in the bone marrow, the amyloid in all other organs stained readily with congo red and the aniline dyes: cresyl violet, methyl violet and aniline gentian violet.

Anatomic Diagnosis.—The following diagnosis was made: amyloidosis of the liver, spleen, pancreas, stomach, thyroid and suprarenal glands; diffuse amyloidosis of the bone marrow with collapse of the ninth thoracic and first lumbar vertebrae; amyloidosis of the kidneys with incipient contraction; edema of the lungs; brown atrophy of the heart; hypertrophy of the left ventricle; healed erosions of the stomach and duodenum.

COMMENT

The diagnosis made during the life of the patient was amyloid nephrosis, hypercholesteremia, hepatomegaly and lipoid histiocytosis. The clinical aspects of the case were reported by Rachmilewitz [5] while the patient was still alive. The subsequent postmortem observations of generalized amyloidosis, with marked involvement of the kidneys and liver, serve to explain the hypercholesteremia and hepatomegaly. No evidence of lipoid histiocytosis was found. Despite a careful search at autopsy no explanation could be offered for the cause of the amyloidosis.

The amyloid deposits in the internal organs, aside from those in the pancreas and kidneys, showed nothing of unusual significance. The infiltration of the pancreas is noteworthy because of the infrequency of this condition. The microscopic appearance conformed to that seen in similar reported cases.

The clinical course of the patient presented a complete picture of amyloid disease of the kidneys beginning with the nephrotic syndrome and terminating with renal insufficiency. The signs and symptoms of

5. Rachmilewitz, M.: J. A. M. A. **93**:604, 1929

nephrosis persisted for a period of more than two years, during which the renal function and the blood pressure were normal. The gradual onset of renal insufficiency and the sudden appearance of hypertension were ascribed to incipient contraction of the amyloid kidneys; this was confirmed by the anatomic observations.

It has been observed frequently that in patients with amyloid contracted kidneys azotemia may develop terminally (Fahr,[6] Noble and Major [7] and Bell [8]). The occurrence of hypertension, on the other hand, has not been noted by the majority of observers (Volhard and Fahr [9] and Rosenberg [10]); they have reported a low tension as a rule. However, Fahr [6] recently asserted that hypertension may be present in young patients if cachexia is absent. He ascribes the infrequency of hypertension in patients with amyloid contracted kidneys to vascular "inadequacy" caused by cachexia, which is often marked in these patients. In these instances the hypertension is thought to be of renal origin. Similarly Bell, Noble and Major and others have reported hypertension with amyloid contracted kidneys and they consider the hypertension to be of renal origin. The case reported in this study seems to support this concept.

As mentioned at the beginning of this report, only scanty vascular infiltrations have been found in the bone marrow in cases of generalized amyloidosis. The nature of the infiltration, in these instances, does not differ from that seen in vascular involvement of other organs. In the present case, however, the amyloid deposits were seen not only in the vessels but also in the reticulum and in the walls of the sinusoids. The infiltration was comparable to that reported in the amyloid tumors of the bone. The latter, however, have many distinguishing characteristics. In contrast to the diffuse amyloid infiltration in the present case, the amyloid is localized as a massive accumulation in one or several bones while the marrow of the other bones is free. There are, however, a number of features common to both the primary amyloid tumors of the bone and the present case.

Eight instances of amyloid tumors of the bone have been reported (Edens,[11] Mandl,[12] Hildebrand,[13] Hedrén,[14] Schmid,[15] Ophüls,[16]

6. Fahr, T.: Klin. Wchnschr. **10**:1205, 1931.
7. Noble, J. F., and Major, S. G.: Arch. Path. **8**:762, 1929.
8. Bell, E. T.: Am. J. Path. **9**:185, 1933.
9. Volhard, F., and Fahr, T.: Die Brightsche Krankheit, Berlin, Julius Springer, 1914, p. 21.
10. Rosenberg, M.: Deutsche med. Wchnschr. **57**:99, 1931.
11. Edens: Virchows Arch. f. path. Anat. **184**:137, 1906.
12. Mandl, J.: Virchows Arch. f. path. Anat. **253**:639, 1924.
13. Hildebrand, O.: Virchows Arch. f. path. Anat. **140**:249, 1895.
14. Hedrén, G.: Ztschr. f. klin. Med. **63**:212, 1907.
15. Schmid, H., cited by Askanazy.[4]
16. Ophüls, W.: J. Exper. Med. **5**:111, 1900.

Wolpert [17] and von Bonsdorff [18]). Two of these, the case of Schmid and that of Hildebrand, were instances of amyloid deposits within blastomas of the bone and should not be classified with the cases of amyloid tumors of the bone. Aside from the present case and the slight vascular involvement occasionally reported in generalized amyloidosis, the amyloid tumors of the bone represent the only other form of idiopathic amyloid disease of the bone marrow. Because of the destructive action of the amyloid deposits these tumors of the bone may give rise to serious symptoms and are often mistaken for blastomas. In all instances the authors described a cellular reaction in the area of the amyloid deposits, together with the presence of granulation tissue and multinucleated giant cells; these were considered to be local reactions to the presence of the amyloid. The alteration of the bone was comparable to that described in the present case. In only one instance was there evidence of vascular occlusion (Mandl); in the other cases the pressure of the infiltrating amyloid was probably responsible for the destruction of bone. This seems to be indicated by the studies in the present case. The most marked destruction of the bony trabeculae was noted in the areas in which the amyloid was present in direct apposition to the bone (fig. 2*A*). Where the marrow cells were still intact along the margins of the bone, that is, where the amyloid had not infiltrated to the bone, there was little or no evidence of destruction of bone. This seems to indicate that the direct pressure of the amyloid gave rise to the alterations in the bone. Neither in this case nor in the amyloid tumors of the bone was there any evidence of the formation of new bone. No explanation has been offered to account for this observation. The amyloid staining reactions in the amyloid tumors of the bone showed variations similar to those described in the present case; the amyloid stained irregularly with iodine and presented marked variations in metachromasia with the aniline dyes.

Amyloid deposits within blastomas or in chronic diseases of the bone or bone marrow are to be distinguished from the amyloid tumors of the bone. In the former conditions the amyloid deposits are considered to be secondary to the involvement of the bone marrow. When a tumor-like appearance is present, in contradistinction to the amyloid tumors of the bone, it is caused by the blastoma rather than the amyloid deposits. The quantity of amyloid present in the blastoma may vary from minute amounts, visible only under the microscope, to large accumulations sufficient to obscure the underlying blastoma. Weber [19] has

17. Wolpert, I.: Virchows Arch. f. path. Anat. (supp.) **227**:173, 1920.

18. von Bonsdorff, B.: Finska läk.-sällsk. handl. **75**:447, 1933; abstr., J. A. M. A. **101**:489, 1933.

19. Weber, H.: Beitr. z. path. Anat. u. z. allg. Path. **86**:1, 1931.

emphasized the necessity of a careful search for the presence of the underlying blastoma; in a case reported by him, the multiple myeloma was found with difficulty. In these instances the destruction of the bone is no doubt primarily due to the underlying blastoma rather than to the amyloid, although the latter may aggravate the process. The staining reactions of the amyloid in blastomas are atypical, showing variations similar to those observed in the amyloid tumors of the bone and in the present case. Klemperer [20] described a case of lymphoblastic myeloma in which there were scattered homogeneous masses that stained deeply pink with eosin and partly yellow and partly red with van Gieson stain, but did not take the usual amyloid stains. It is possible that this was an instance of achromatic amyloid.

The blastomas most frequently showing secondary amyloid deposits are the multiple myelomas. Cases have been described by Weber, Glaus,[21] Hueter [22] and others. The relatively frequent association of this type of blastoma with amyloid deposits, both in the blastoma and in the viscera, has received the attention of many observers, who see in this association a pathogenetic relationship. Magnus-Levy [23] considers the Bence-Jones protein, occurring frequently in multiple myelomas, as the matrix of the amyloid. To advance his concept further, he suggests that the primary amyloid tumors of the bone are instances of multiple myeloma with secondary amyloid deposits rather than idiopathic amyloid tumors, the amyloid having arisen from the Bence-Jones protein. He likewise suggests that the amyloid deposits may, in these instances, have obscured the underlying blastomas, as Weber noted, or that the authors overlooked the underlying tumor as, for example, in Ophüls' case in which the amyloid deposits were considered to have arisen in a gummatous osteitis of the bones and were described by Ophüls as areas of plasma-like cells in the amyloid masses. There is nothing in the descriptions of the other cases of primary amyloid tumors of the bone, however, that indicates the presence of an underlying blastoma. The aforementioned authors stated that after careful search no evidences of tumor were found.

The diffuse distribution of the amyloid in the marrow readily distinguishes the present case from the other forms of amyloidosis of the bone marrow. Contrary to the observations in amyloid tumors of the bone, no inflammatory reaction was present despite the extensive destruction of the bones and the marked atrophy of the marrow. The involvement of the marrow was undoubtedly responsible for the secondary anemia observed in the later stages of the patient's illness. The

20. Klemperer, P.: Beitr. z. path. Anat. u. z. allg. Path. **67**:492, 1920.
21. Glaus, A.: Virchows Arch. f. path. Anat. **223**:301, 1917.
22. Hueter, C.: Beitr. z. path. Anat. u. z. allg. Path. **49**:101, 1910.
23. Magnus-Levy, A.: Ztschr. f. klin. Med. **116**:510, 1931.

collapse of the vertebrae is comparable to that described in the case of amyloid tumor of the bone of the third thoracic vertebra reported by Mandl, in which pressure on the spinal cord had led to compression myelitis. It is not unlikely that in this patient the pressure of the collapsed vertebrae on the nerves as they emerged from the intervertebral foramina was responsible for the muscular pains in the lower part of the abdomen.

A careful study of the present case indicates that the amyloid deposits were not secondary to an underlying blastoma. In the mass of amyloid, even where the destruction of the bone was most extensive, the surviving marrow cells showed a normal ratio of myeloid and erythropoietic cells; no tumor cells were noted. Also the diffuse involvement of the marrow speaks against the presence of an underlying blastoma. However, because of the case reported by Freund,[24] it was necessary to consider the controverted concept of diffuse myeloma with secondary amyloid deposits. The presence of normal hematopoietic tissue throughout the marrow militates against this interpretation. The present case is clearly an instance of idiopathic diffuse amyloidosis of the bone marrow and viscera.

The rarity of amyloid infiltrations in the bone marrow has not been explained. Magnus-Levy offers an interpretation in the fact that the circulation of the marrow is constant and that, unlike the spleen and liver, it is not an expansile organ, so that the "pressing in" of circulating amyloid into the tissue spaces of the bone marrow is not favored. However, if the bone is the seat of a destructive process, as in blastomas, stasis ensues, and the deposition of amyloid is facilitated. This interpretation can account for only some of the physical factors, as Magnus-Levy himself acknowledges. It cannot, however, be applied to instances in which destruction of the bone was not present prior to the amyloid deposition, as in the present case.

SUMMARY

In addition to the three described forms of amyloid deposits in the bone or bone marrow, namely, isolated instances of vascular infiltration in generalized amyloidosis, primary amyloid tumors of the bone and secondary amyloid deposits within blastomas or other diseases of the bone, a fourth type is added, that of diffuse amyloidosis of the bone marrow associated with generalized amyloidosis. No similar case was found in a survey of the literature. No cause for the amyloidosis was found.

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24. Freund, E.: Frankfurt. Ztschr. f. Path. **40**:400, 1930.

A PRINCIPLE ACCELERATING GROWTH AND MATURATION

DEMONSTRATED IN METASTASES OF A TUMOR OF THE THYROID GLAND

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The physiologically active principle characteristic of the parental tissue has been demonstrated in a variety of tumors. Thus, epinephrine was demonstrated by the frog's eye method and chemically in medullary tumors of the suprarenal gland by Orth,[1] Wiesel and Neusser,[2] Wegelin,[3] Hedinger,[4] Raben [5] and Schultz [6] and by the effect on blood pressure by Hick.[7] Plaut [8] demonstrated the presence of thyroxine in thyroid gland rest tumors of the ovary by the acetonitril (Reid Hunt) and the tadpole maturation (Gudernatsch) tests. Heller [9] and many others observed bile in the metastases of hepatocellular carcinomas of the liver. Similarly, certain clinical observations suggest that tumors may display the functional properties of the parental tissue. In this category fall the Langhans cell tumors with hyperparathyroidism,[10] the oxyphilic and basophilic adenomas of the hypophysis [11] and the gonadal tumors with their respective syndromes dependent on the elaboration of the principle characteristic of the tissue from which they originate. The demonstration of prolan A in the urine in teratoma testis [12] and that of intermedin in the urine in neurogenic tumors and melanomas [13] are of even more direct significance. Similarly, Ewing [14] mentioned

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1. Orth, K.: Preuss. Akad. Wissensch. **2**:34, 1914.
2. Wiesel, J., and Neusser, E.: Die Erkrankungen der Nebennieren, Vienna, M. Perles, 1910, p. 27.
3. Wegelin: Verhandl. d. deutsch. path. Gesselsch. **15**:255, 1912.
4. Hedinger, E.: Frankfurt. Ztschr. f. Path. **7**:112, 1911.
5. Raben, C. B.: Arch. Path. **7**:228, 1929.
6. Schultz, W. H.: Am. J. Physiol. **90**:508, 1929.
7. Hick, F. K.: Arch. Path. **15**:665, 1933.
8. Plaut, A.: Klin. Wchnschr. **10**:1803, 1931.
9. Heller, cited by Ewing.[14]
10. Jaffe, H. L.: Arch. Path. **16**:63 and 232, 1934.
11. Cushing, H.: Bull. Johns Hopkins Hosp. **50**:137, 1932.
12. Ferguson, R. S.: Am. J. Cancer **18**:269, 1933.
13. Ferguson, R. S.: Am. J. Cancer, to be published.
14. Ewing: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928, p. 53.

absence of symptoms of Addison's disease in a patient with a massive hypernephroma and apparently complete destruction of the suprarenal glands. In this instance the evidence is not so certain, since aberrant suprarenal tissue is common and symptoms do not develop in the presence of excessive amounts of cortical substance.

Ewing summarized this subject by stating that the functional activity displayed by tumors diminishes with increasing anaplasia. Any amount of function from overactivity to complete absence of activity may be met with.

The pathologic entity variously referred to as metastasizing thyroid gland, metastasizing goiter or metastasizing adenoma has been thoroughly studied from the morphologic standpoint and, indeed, the various names applied to it serve to indicate its malignant character as observed grossly and clinically, and its benign character as observed histologically. Engelstad [15] demonstrated active thyroid substance in the metastases of a carcinoma of the thyroid gland by the acetonitril test. In the present article I shall present evidence of a substance promoting growth and maturation which was present in the metastases of a tumor of the thyroid gland, the primary growth of which was histologically malignant, though at autopsy the thyroid tissue present and the metastases as well were histologically benign.

REPORT OF CASE

In 1920 a white woman, 49 years of age, noted a slight enlargement on the anterior surface of the neck, which increased to the size of a hen's egg during the following two years. During the third year the mass began to increase rapidly and the patient complained of a choking sensation when she attempted to swallow. During this period she lost about 10 pounds (4.5 Kg.), but did not complain of nervousness, intolerance of heat or other features characteristic of hyperthyroidism. She entered the Cook County Hospital on July 4, 1923, at which time the right lobe of the thyroid gland was enlarged to the size of a grapefruit. It was firmly fixed to the surrounding structures and moved only slightly during swallowing.

Lobectomy was performed and sections of the tumor were examined microscopically. The growth was diagnosed as carcinoma of the thyroid gland.

Roentgen examination of the chest, spine and long bones failed to demonstrate metastases.

The patient was readmitted in June, 1932 (nine years after the original admission and twelve years after the onset of symptoms). At this time she complained of sacro-iliac pain. An x-ray picture revealed metastases in the sacrum. Six months later (Jan. 19, 1933) she again returned to the hospital with a history of having had headaches and "pistol shot" noises in the head for eight years, a swelling in the right parietal region for four years, and weakness and dyspnea becoming progressively more pronounced for several months.

She was extremely emaciated. A soft, smooth elevated, pulsating mass, 12 cm. in diameter, was present in the right parietal bone. A ragged edge, apparently

15. Engelstad, R. B.: Ztschr. f. Krebsforsch. **39**:369, 1933.

bone, was palpated about the margin of this mass. A loud bruit was heard over the dilated and tortuous temporal vessels, and similar but softer sounds were audible over the tumor itself. The vessels on the right side of the neck pulsated, and over them a thrill was felt and a bruit heard. The heart was enlarged and a double murmur was heard over the apex. The upper region of the right lung gave a dull sound on percussion, and the breath sounds were of diminished intensity and associated with sibilant râles. The basal areas posteriorly gave a dull sound and here many moist râles could be heard. The finger tips were clubbed and cyanotic.

The veins in both fundi were engorged, and papilledema was noted on the right.

The laboratory findings were insignificant.

A rapidly downward course terminated in death on January 25 (six days after admission).

Autopsy.—Dr. R. H. Jaffé made the following observations eight hours after the death of the patient. The external findings were essentially as described in the foregoing paragraphs.

The pleural cavities were partially obliterated by dense adhesions, and each contained about 100 cc. of clear fluid. The lungs were distended and heavy, and the pleural surfaces were covered with fibrous tags. The surfaces were studded with firm, light purple-gray nodules, varying in size from that of a pin-head to 20 mm., the larger of which displayed central umbilication. Similar masses were scattered throughout the lung and, as seen on the cut surface, were separated by moist, light purple-gray to purple-brown pulmonary tissue.

The pericardial sac contained 100 cc. of clear fluid. The heart weighed 415 Gm. The myocardium was pale and friable. Atheromatous and calcareous plaques were scattered over the inner surfaces of the coronary arteries and aorta.

The left lobe of the thyroid gland weighed 35 Gm. The color varied from light purple-gray to grayish brown. The cut surface was made up of nodes from 20 to 30 mm. in diameter and it varied in color from light brown to yellowish brown. To the right of the trachea in place of the right lobe of the thyroid gland was found a firm, confluent mass of spherical nodes 8 by 5 by 4.5 cm. in diameter. The sectioned surface of this mass was light purple-gray mottled with grayish white.

In the fundus of the stomach at the greater curvature was a firm submucous nodule 25 by 15 by 10 mm. in diameter.

The mass noted on the external aspect of the skull was found to extend through the bone and to be firmly adherent to the dura. The edges of the bony defect were indented and friable. A similar mass protruded into the pelvis from the lower half of the sacrum.

Microscopic Examination.—In the thyroid gland the follicles were generally small, lined by epithelium varying from flat to cuboid and largely isolated into nodules by a dense hyaline and, in some areas, calcified stroma. In certain areas the follicular epithelium contained blood pigment. The superior thyroid artery and its branches displayed marked calcification. The veins were distended, but no fragments of the tumor were found in the lumens.

In the lung the nodules seen grossly were sharply demarcated from the surrounding compressed and, in some areas, blood-filled alveoli. They consisted of a delicate vascular stroma and numerous small follicles resembling those seen in the nodules in the thyroid gland. The smaller follicles had practically no lumens; in the larger ones the lumens were empty or filled with pale-staining homogeneous

material. The cells lining the follicles were uniform in size, shape and staining qualities. Hemorrhage was seen in the centers of some of these metastatic nodules.

The peritracheal lymph nodes showed follicle-like structures separated by a varying amount of stroma replacing the normal lymphatic tissue. The follicles were lined by cylindric epithelium displaying a moderate degree of papillary infolding.

The metastases to the parietal bone presented essentially the same histologic picture as did the pulmonary metastases.

A nodule from the region of the gastric fundus was examined. The mucosa was thickened. It was made up of long, slender glands lined by regular, clear cylindric epithelium and other irregular, branched structures formed by large cells with hyperchromatic and anaplastic nuclei as well as dilated glandlike structures the lumens of which were filled with pus cells and lined by low cylindric epithelium. Single glands extended through to the serosa. The stroma was rich in small round cells and plasma cells.

Anatomic Diagnosis.—The anatomic diagnosis was: metastasizing goiter involving both lungs, the right peritracheal lymph nodes, the parietal bone and the sacrum; ancient lobectomy of the right lobe of the thyroid gland; early carcinoma in adenomyoma of the stomach; chronic tumor of the spleen; moderate hypertrophy of the heart; parenchymal degeneration of the liver, myocardium and kidneys; mucous colitis and bilateral hydrothorax.

EXPERIMENTS

Several days after the death of the patient the nodules of the tumor were dissected out of one lung. They totaled 250 Gm. in moist weight. They were run through a meat grinder, spread on glass plates and dried in a stream of warm air. On April 23, 60 mg. of this dried material was added to the fish food placed in each of two pans, one containing seventy and the other forty-five tadpoles. This daily ration of material from the tumor was continued until July 13. Several variable-sized groups of tadpoles from the same batch of eggs were retained as controls and fed only fish food or fish food plus dried beef heart. The experimental group and the controls were killed with chloroform on July 13, and the maximum length of each tadpole was measured and the animals were photographed (figs. 1, 2 and 3).

The mean and the standard deviations were calculated according to the formulas described by Pearl.[16]

In the control group of eighty-four tadpoles, the mean length was 2.39 ± 0.036 cm., and the standard deviation was 0.49 ± 0.025 cm. Group 1 of the tumor-fed tadpoles with sixty-four survivors at the end of the experiment had a mean length of 3.64 ± 0.1 cm., with a standard deviation of 1.19 ± 0.071 cm., and, in addition, six fully developed frogs and one tadpole with hindlegs at the termination of the experiment. Similarly, group 2 of the tumor-fed tadpoles with forty

16. Pearl, R.: Introduction to Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1930, chap. 13, p. 264.

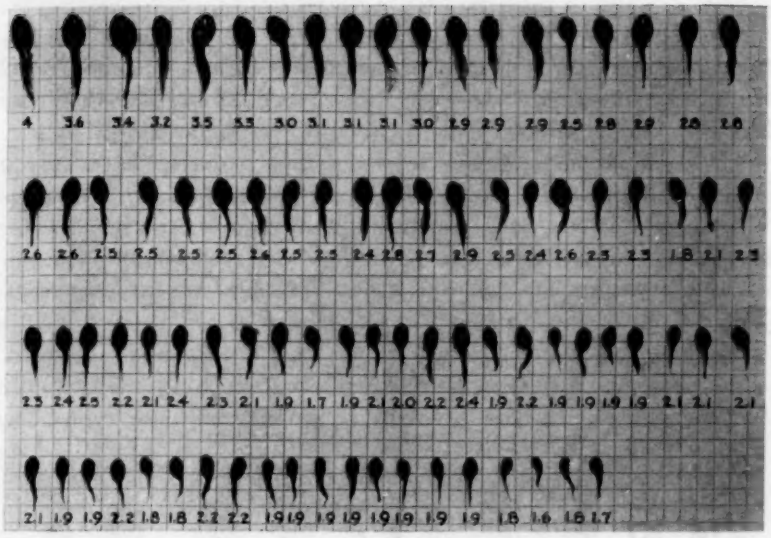

Fig. 1.—Control group of normal tadpoles. They were fed fish food ad libitum from April 25 until July 13, when the survivors (eighty-four) were killed. The numbers represent the individual tadpole lengths in centimeters. The mean length was 2.39 ± 0.036 cm. The standard deviation was 0.49 ± 0.025 cm.

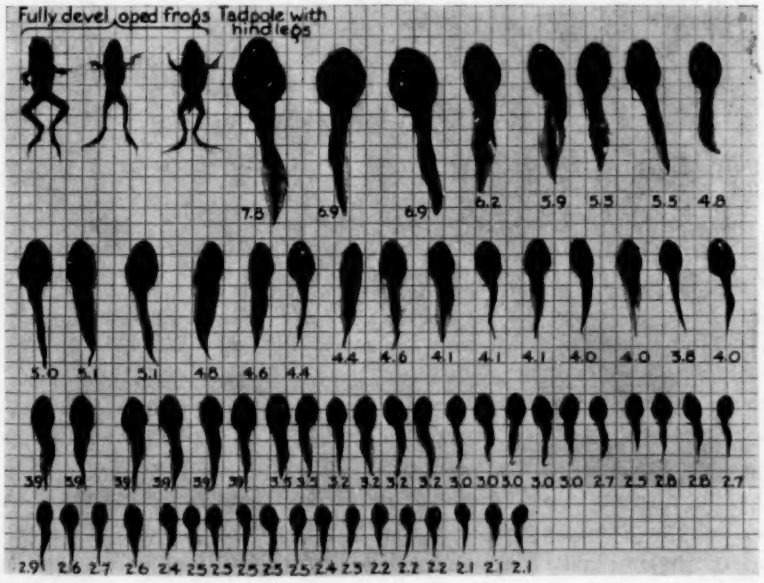

Fig. 2.—Group 1 of the tumor-fed tadpoles. They were fed fish food plus 1 grain (0.06 Gm.) of tumor substance daily from April 25 to July 13, when the survivors (sixty-four out of seventy-five) were killed. The numbers represent the individual tadpole lengths, in centimeters. The mean length was 3.64 ± 0.1 cm. The standard deviation was 1.19 ± 0.071 cm. Three frogs developed and died between June 21 and 27 (not photographed).

survivors at the end of the experiment had a mean length of 5.19 ± 0.119 cm., with a standard deviation of 1.112 ± 0.084 cm. Three fully mature frogs and four frogs with tails retained developed in this group.

Thus the control group showed a standard deviation of only 0.49 cm., indicating a uniform and rather narrow distribution of sizes about the mean of 2.39 cm., and no maturation during the experimental period. Group 1 of the tumor-fed group with a standard deviation of 1.19 cm. about the mean of 3.64 cm. and group 2 with a standard deviation of 1.112 cm. about the mean of 5.19 displayed a much more rapid and variable rate of growth. The time of maturation, as is indicated by the development of fully or partially matured frogs in these two groups, was also accelerated. The difference in growth and maturation between

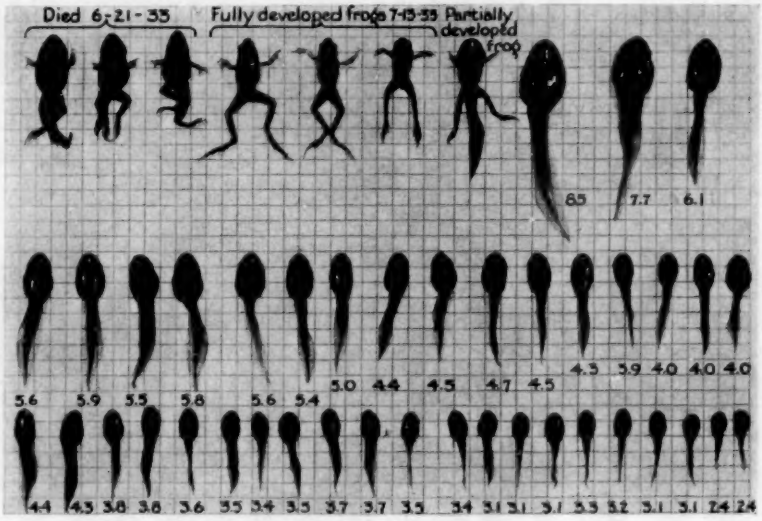

Fig. 3.—Group 2 of the tumor-fed tadpoles, given the same rations over the same period as group 1. Forty out of forty-five survived. The mean length of the survivors was 5.19 ± 1.19 cm. The standard deviation was 1.112 ± 0.084 cm.

the two tumor-fed groups is explainable by the difference in the number of tadpoles in the two groups, the smaller group showing the most rapid growth and maturation.

The variations within the group are explainable by differences in the individual intakes and differences in the developmental potentialities of the individual tadpoles. Which of these factors was the chief or perhaps the sole element could have been settled only by placing one or two tadpoles in each experimental pan instead of the large numbers used.

Because of the length of time intervening between the death of the patient and the preparation of the dried material of the tumor, quanti-

tative estimates of the potency of this substance would have been futile. However, 0.06 mg. of commercial desiccated whole thyroid gland given daily killed a pan of tadpoles within one week whereas the number killed by 0.06 Gm. of the tumor substance, while higher than the number dying among the controls, was only a small fraction of the total number of tadpoles given this dose.

These findings allow the conclusion that the metastases of the tumor of the thyroid gland contained a principle that accelerated the growth and maturation of the tadpoles.

SUMMARY

Experimental evidence is presented that there exists in the metastases of tumors of the thyroid gland a principle that accelerates the growth and maturation of tadpoles.

THE INHERITANCE OF FOCAL MELANOSIS IN DROSOPHILA

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PRINCETON, N. J.

In a study of the physical characteristics of the gene,[1] adult male drosophilas were exposed to one minute irradiation with roentgen rays from a copper target tube. Eight thousand nine hundred and twenty electrostatic units were given per minute per square centimeter in 1 cm. of air by this tube. These males were bred to females having in one chromosome the familiar C1B factor combination. The female progeny containing as their sex chromosomes the C1B of the mother and the irradiated X of the father were bred in single cultures to males having sex chromosomes containing the genes for white eye color and miniature wings. The progeny of one such mating, 16546 A-20, were fifty wild type and fifty-four Bar females and two males. Both males showed black melanotic spots on the second joint of the legs. They walked stiffly and easily became stuck in the culture mediums. These males were bred to their wild sisters which carried the mutant gene. There resulting progeny included a very few females, as well as males, which had black spots on the second joint of the legs. The normal wild type male and female of Drosophila are shown in figure 1 *A* and *B*. Two females and a male showing the degenerated leg joints are shown in figure 1 *C*, *D* and *E*.

A sex-linked lethal gene kills off all the males which receive it, or one half of the total male progeny. In most instances no trace of these males is discovered. The existence of a lethal gene is inferred from the fact that a genetic class which should occur is missing. In the case described in this report a few of the males carrying this gene are not badly affected and survive. They represent only a small proportion of the expected males. In the initial case in which there were fifty wild type and fifty-four Bar females there should have been fifty males having lesions to correspond with the fifty wild type females, whereas only two survived. Examination of the culture bottle revealed the bodies of the rest of these males, each one showing pronounced lesions.

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1. Gowen, John W., and Gay, E. H.: Gene Number, Kind and Size in Drosophila, Genetics **1**:1, 1933.

The males having this sex-linked gene had been able to crawl out of the pupa case but, unable to move normally, had died. The paper at the bottom of the bottle covered with these dead males is shown in figure 1, *F*. Sixty-two males showing lesions of the joints were found dead on the paper. When they were all counted the males were of sufficient number to balance the female class, as they should be to meet genetic expectations.

The extent to which degeneration may go is shown in figure 1 by the size of the blackened area which replaced the leg joints. This degeneration apparently develops at the time the fly leaves the pupa case, since melanotic lesions were not noted in flies of the proper genetic constitu-

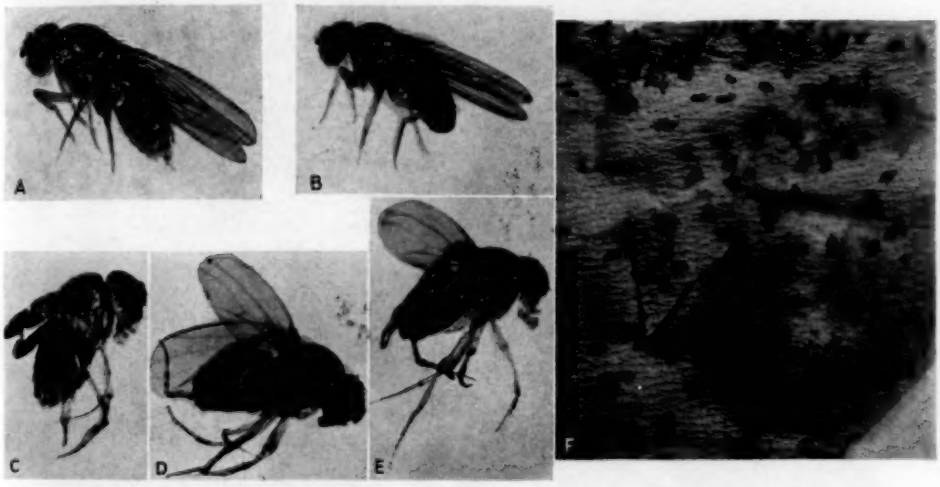

Fig. 1.—Normal wild type male and female for comparison with males and females showing lesions of the leg joints, an inherited pathologic condition produced by a gene. Roentgen treatment of the wild type gene of the wild type normal flies shown in *A* and *B* caused a change into a gene producing the condition shown in *C*, *D* and *E*. The males which show the effects of this gene generally die. In *F* their bodies are seen scattered over the paper which covered the bottom of the bottle in which they emerged from their pupa cases.

tion dissected from the pupa cases. The lesions do not show any increase in area with the aging of the fly. There is no evidence of continuous growth.

The amount of tissue included in the focal melanosis varies from culture bottle to culture bottle, environmental conditions such as moisture playing a rôle in the expression of this gene. In its host expression the blackened necrotic area may appear as only one slight spot on the lower tip of the femur or upper end of the tibia. In its more extreme

condition all the legs may be involved, the necrotic degeneration including half the femur and tibia on either side of the joint. No melanosis of any of the other joints, as those between the tarsae or coxa, trochanter and femur, takes place. Figure 2 shows three leg joints displaying these lesions; the joint in 2 *A* has quite a limited melanosis, that in 2 *B* is more extreme, and in 2 *C* the melanosis involves about one third of both the femur and the tibia.

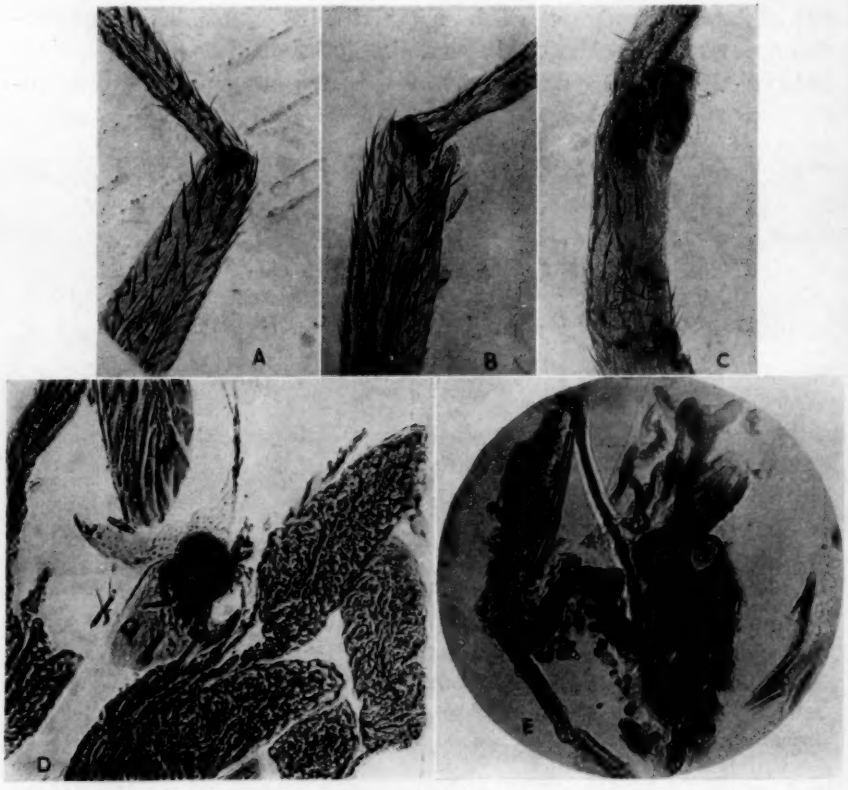

Fig. 2.—Various types observed in the focal melanosis of the leg joint. *A* shows but slight melanosis; *B* shows a more extreme, and *C* a still more complete, involvement of the leg. *D* and *E* are photographs of sections through these joints. *D* is a section stained with eosin. As the melanotic area is pigmented black with insoluble pigment it appears black in the photograph. *E* is a section at a higher magnification and is stained with iodine gentian violet, a nuclear stain. Again the melanotic area is black owing to the pigment.

High power magnification of sections through the necrotic areas shows that the region of functional failure and degeneration is at the junction of the tibia and femur. The degeneration includes the cuticula and the underlying ectoderm. The muscles do not appear to be involved

except in the lesions in which degeneration is extensive, when the whole femur and tibia may be reduced to a structureless mass of melanotic tissue. In such cases muscular atrophy appears to be a secondary change brought about by the antecedent cuticular degeneration.

The chemical solubilities [2] of the black pigment left after degeneration of the tissues are of interest as they give some idea of its nature. Soaking the specimens for a period of two years in water, weak hydrochloric acid, ethyl alcohol, ether, xylol, carbon bisulphide, glycerin, glacial acetic acid, purified petroleum benzine and solutions of calcium hydroxide and barium hydroxide failed to dissolve the pigment. It is readily soluble in a 5 per cent solution of sodium hydroxide, leaving a clear chitinous shell. It is also soluble, with some difficulty, in concentrated nitric acid, the chitinous shell dissolving as well as the black pigmentation. To this extent, then, the degeneration may be regarded as replacing much of the tissue with a substance having the general properties of melanin.

The technic used to detect mutations produced by roentgen rays showed the gene causing this focal melanotic degeneration to be sex-linked. Its further linkage relations are shown in the following tabulation.

Parents ♀ $\frac{y_1 w_2 m_3 B_x}{me}$ x ♂ y cv v f		
	Progeny	
Genetic constitution		
noncrossovers	Without melanotic lesions	With melanotic lesions
y w m Bx	157	
+	7	27
Single crossovers		
y		
w m Bx	3	
y w		1
m Bx	4	1
y w m	7	
Bx		1
Double crossovers		
y m Bx		
w		
y Bx		
w m		
y w Bx		
m	2	

The data list the males only. Of the alternate classes for each crossing over, the classes showing the yellow gene are given first. Crossing over in the presence of this gene has obviously been seriously reduced.

2. Abel, J. J., and Davis, W. S.: On the Pigment of the Negro's Skin and Hair, J. Exper. Med. **1**:361, 1896.

The evidence shows the gene to be between white and miniature, near miniature. Crosses including the factors y cv v f show a like result.

Parents ♀ $\frac{me}{y_1 cv_2 v_3 f}$ x ♂ y cv v f

Progeny

Genetic constitution	♂'s Without melanotic lesions	♂'s With melanotic lesions	♀'s Without melanotic lesions
Single crossovers			
noncrossovers			
y cv v f	258		197
+	1	12	213
y			1
cv v f	1		1
y cv			1
v f	2		
y cv v	7		8
f		1	6
Double crossovers			
y v f			
cv			
y f			
cv v			
y cv f			
v			

The inherited factors other than the factor for the focal melanosis, *me,* are the familiar ones: yellow (y), white (w), miniature (m), Beadex (Bx), cross-veinless (cv), vermilion (v) and forked (f), distributed along the length of the sex chromosome.

The data in the foregoing tabulation agree with those of the previous cross in showing the gene's locus to be at the left of vermilion and near it. So far as the flies which may be counted as live adults are concerned, it acts nearly as a lethal factor. It is evident that the chromosome change also markedly affects the rate of crossing over, the amount being reduced from 56 per cent for the yellow to forked region to only 4 per cent. The crossing over rate in the yellow to vermilion region is normally 33 per cent. In the presence of the gene, tentatively designated as *me,* it is reduced to 0.7 per cent. The vermilion to forked region suffers a reduction to 3.3 per cent from a normal of 23 per cent. This reduction in crossing over is not primarily due to the gene for melanotic lesions as is shown from data on an independent mutation produced by roentgen rays in the same locus. This second mutation came as the result of a later experiment with roentgen rays. Males containing mature sperm were treated with 26,620 electrostatic units from a chromium target tube. These males were bred as in the first experiment. The F_2 male progeny showed the same black pigmented spots as those of the first mutation. In all respects the somatic effects of this gene

resembled those of the first. Flies containing the second gene were crossed with those having the first gene. The progeny showed the genes to be the same or at least allelomorphic. The linkage test showed the following crossover values with yellow cross-veinless vermilion forked. The yellow to cross-veinless crossover ratio was 9.4 per cent; cross-veinless to *me*, 17 per cent; *me* to vermilion, 3.8 per cent, and vermilion to forked, 28 per cent. Considering the total amount of the data, sixty flies, all of these percentages are well within the standard values. The locus of the gene for the focal necrosis of the femur-tibia joint may consequently be placed in the sex chromosome at 29. This locus corresponds with that of another gene, described some years ago as producing a somewhat similar effect. This ascutex gene was located at 28 units.

The mode of inheritance of focal melanosis of the leg joints has made it possible to maintain the disease for over one hundred generations of progeny since the first fly with lesions appeared. During this time no fly showed any trace of the lesion unless it carried the genetic constitution for it. As in every culture bottle about half the population was without the gene producing focal melanosis, this half acted as normal controls for the other half having it and showing it by the lesions of the leg joints; it follows that interpretation of the disease as contagious is ruled out.

That the melanosis is dependent on the proper genetic constitution of the given body cells is critically demonstrated by a fly representing an accident of development. The left side of this fly was male and had only one sex chromosome which chanced to carry the gene for this melanotic degeneration of the joints. The right side of the fly was female and had two sex chromosomes, one carrying the gene for the focal melanosis, the other having the yellow, white, miniature and Beadex factors as well as the normal allelomorph of the focal melanosis gene. In crosses the focal melanosis gene behaves as a recessive. One would therefore expect that since it is homozygous on the left, or male side, of the fly that focal melanosis would be noted on this side. Such lesions were found, the melanosis on the second and third legs being rather extreme. Similarly on the female side, where the cells are only heterozygous for the focal melanosis gene, one would expect no lesions. Careful examination of the femur-tibia joints showed them to be perfectly healthy. The fortunate loss of the yellow, white, miniature Beadex chromosome from half of this fly's body has thus shown clearly the dependence of focal melanosis on the genetic constitution of the particular cells in the region where degeneration is to take place.

COMMENT

Focal melanosis of the femur-tibia junction in these flies has been shown to have its ultimate etiology in a single sex-linked factor. This gene's locus within the chromosome is about 29 units from the left end.

The disease-producing factor appeared as a result of a specific alteration in gene material located within a minute region of the sex chromosome. The agent initiating these changes was roentgen rays from copper in one case and from chromium in another. The melanosis is completely suppressed in the heterozygous animal by the action of the normal allelomorphic gene within the nuclear structure of the same cell. In a fertilized egg this gene for focal melanosis is presumably carried to each cell of the developing embryo by the successive divisions of the cell. It reacts only at the time when the processes of differentiation are essentially completed as a specific degeneration of a given group of cells. Since such a gene is capable of being carried to any of the future generations of progeny by breeding, it follows that the focal melanosis has unlimited possibilities of spread in the population.

This statement of the conclusions to be drawn from the evidence for the germinal origin of the lesions seems clear. The manner in which the gene acts in the embryologic development of the organism is not so evident. From examination of the formed fly as it is found in the late stages of pupal development one finds no traces of the melanotic focal lesions grossly evident in the imago. There may be some slight thinning of the legs at the joints, but there are no obvious lesions. The condition appears to arise rather suddenly at or near the time of emergence of the fly from the pupa case. Flies which show the lesions when kept alive for a period of time show no growth of the involved area. From these facts the case for the embryologic changes involved may be regarded somewhat as follows: The normal potentialities for growth differentiation of the leg joints are present and are exercised in the embryologic development of the affected flies. These tissues when formed have a defective vitality owing to the presence of the gene under discussion. In the stress of emergence from the pupa and in favorable environmental conditions the defective tissue of this strictly localized area is changed to form the pigmented residue noted as the end-product of the reaction. Such changes, while they strike the imagination because they are disease-producing, are not new. Like changes of the end-products of gene control in embryologic development are familiar enough in normal development as, for instance, the differentiation of no pigment versus brown pigment in the eye of man. It is not commonly seen in cases like that described here, owing, I presume, to the fact that, should the lesions involve vital organs in the early development, little or no trace of the embryo would be left to study. As indicated elsewhere [3]

3. Gowen and Gay.[1] Morgan, T. H.; Bridges, C. B., and Sturtevant, A. H.: The Genetics of Drosophila, The Hague, M. Nijhoff, 1925, p. 10. Muller, H. J.: The Problem of Genic Modification, Proc. 5th Internat. Genetics Cong., Ztschr. f. indukt. Abstammungs-u. Vererbungsl. (supp. vol.) **1**:234, 1928.

it is just such cases which are most frequently noted in the gene mutations studied in genetic research.

The study of intra-uterine amputations in man leads Streeter [4] to like views, although in those cases the evidence for the genetic nature of the defects cannot be made so precise owing to the technical difficulties of the material. The embryologic evidence leads to the view that these amputations are of germinal origin. In these cases sharply circumscribed areas of limb-bud tissue are of such inferior quality that only imperfect histogenesis occurs. These areas maintain themselves only in the earlier weeks of pregnancy. By the fourteenth week they are fibrous moribund masses, and when these slough away, the limbs show depressions, grooves or healed stumps.

Similar focal deficiencies have been noted in cattle. Hadley [5] has shown that the progeny of certain animals of the Johanna and Sarcastic Lad families of Holstein-Friesian cattle produce offspring with congenital epithelial deficiencies. These deficiencies tend to be localized in the extremities. Frequently the epithelium is not intact below the knees or hocks or on the muzzle, mucous membrane of the nostrils, tongue, hard palate and cheeks. The ears and dew claws are often deformed. Animals with this defective epithelium are unable to survive, since bacteria easily penetrate the open surfaces and produce fatal septicemia. The genetic data indicate that this type of focal deficiency is due to a single mendelian factor.

Focal deficiencies may include constituents of a circulating tissue as well as those of the fixed tissues. Such a deficiency occurring in mice was formerly thought to be completely lethal [6] but has since been shown by De Aberle [7] to be a focal deficiency of the hemoglobin of the blood. The mice having the genetic factor for this deficiency in a homozygous condition have only about a third the hemoglobin present in the blood of normal mice. The deficiency brought about by this gene may be obviated in part by the injection of normal blood into the mouse with a defective genetic constitution, as shown by Gowen and Gay.[8]

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4. Streeter, George L.: Focal Deficiencies in Fetal Tissues and Their Relation to Intra-Uterine Amputations, Washington, D. C., Carnegie Institution, 1930, publ. 414, p. 1.

5. Hadley, F. B.: Congenital Epithelial Defects of Calves, J. Hered. **18**:487, 1927.

6. Little, C. C.: The Inheritance of Black-Eyed White Spotting in Mice, Am. Naturalist **49**:727, 1915.

7. De Aberle, S. B.: Hereditary Anemia in Mice and Its Relation to Dominant Spotting, Am. Naturalist **59**:327, 1925.

8. Gowen, John W., and Gay, E. H.: Physiological Factors Necessary to Alleviate Genetic Lethal Anemia in Mice, Am. Naturalist **66**:289, 1932.

The cases which seemingly most nearly parallel that described here are those of tumors in larva and adult Drosophila as described by Stark.[9] Two different tumor-like growths have been described. The first of these is characterized as an irregular darkly pigmented growth of epithelial origin. The cells near the center are large, polyhedral, spheroidal or fusiform. Pigment is present both within and outside the cell. Toward the periphery the cells become flattened and closely crowded together, forming laminated layers of pigment giving to the tumor the appearance of encapsulation. The growths may occur in the proventricular ganglion, salivary glands or imaginal rudiments of the thorax and abdomen. Larvae carrying these growths never survive to pupate. The ultimate agent which causes the growths to appear is a gene, lethal *7*, located at 0.3 in the sex chromosome. It is limited to flies which have the proper genetic constitution, no evidence for any secondary effect of an outside pathogen being manifest.

This case of lethal *7* differs from focal melanosis of the femur-tibia joint in having a much wider range of foci in which its effects may manifest themselves. The tumor condition is quite toxic; larvae showing the tumor seldom live more than fifteen hours, whereas flies with the focal melanosis of the leg joints live for quite a long period, providing the lesion is not so extreme as to prevent locomotion. The pigment tumors produced by the lethal *7* gene show a continuous increase in size while under observation. The lesions of the leg joints, on the other hand, appear to remain of the same size once they are produced.

The second growth studied by Stark [9] is a benign tumor dependent for its expression chiefly on two genes, one in the third chromosome and one in the second chromosome. These pigmented growths may occur in any segment of the larva. The cells are rounded or polygonal and pigmented. If, perchance, the tumor cells happen to invade the imaginal disks of the appendages, they check the development of these parts. A larva showing the growth may pupate, emerge as an adult, and still carry the tumor. The growth visibly increases in size.

In a number of their effects these growths resemble those of the focal melanosis of the leg joints as here described. There are, however, equally important differences which are, I believe, sufficiently marked to suggest a different mode of action for the genes producing the defects. The fact that the lesions of the femur-tibia joint appear after the fly emerges as an adult, when it is known that the joint is completely formed in the pupa, suggests a distinctly different process from that seen in the abnormal growths of lethal *7*, etc. This view is strengthened by the fact that the lesion, although variable in extent, does not seem to

9. Stark, M. B.: An Hereditary Tumor in the Fruit Fly, Drosophila, J. Cancer Research **3**:279, 1918.

alter its size when flies having it are isolated and kept for two or three weeks. The fact that when examined in the pupa this joint appears thinner than normal—although apparently normal in its tissues—gives still further weight to this view. The chain of observations suggests that this gene causes the formation of cuticular tissue of inferior quality, although apparently normal in appearance, and that this tissue, in the strain and stress of emergence from the pupa case, alters its course of development, giving focal degeneration of the leg joints. The parallel seems to be greater between this lesion and those observed in man by Streeter [4] than between it and the tumors described by Stark.

SUMMARY

This report presents a study of a focal melanosis of the femur-tibia articulation in Drosophila melanogaster. The focal melanosis is induced through the action of a gene located in the middle portion of the sex chromosome, 29 units, mutated twice by roentgen rays, once by 8,920 electrostatic units from a copper target tube and again by 26,620 electrostatic units from a chromium target. The lesion is grossly evident in the imago shortly after emergence, as a dark melanotic degenerate mass at the articulation of the femur and tibia. The effect is somewhat variable. It may involve one or all the legs to a variable extent. Flies having the focal melanosis are usually found dead. The condition is in no way contagious to other flies. Sections show that the melanotic areas are localized at the ends of the femur and tibia in the cuticular layer and its underlying ectoderm. In chemical solubilities the black pigmented masses left in the tissue degeneration behave like melanin pigment.

THE AGE OF PREGNANCY

HISTOLOGIC DIAGNOSIS FROM PERCENTAGE OF ERYTHROBLASTS IN CHORIONIC CAPILLARIES

C. S. RYERSON, M.D.
AND
S. SANES, M.D.
BUFFALO

A simple, reliable method of estimating the age of pregnancy from histologic examination of placental fragments would satisfy more than the mere academic interest of the pathologist. Its medical and legal benefits appear obvious. Various methods reported in the past have apparently missed application in routine laboratory work because of their dependence on qualitative criteria as standards of comparison, unvarying technic in the preparation of material and individual experience in judgment. Variations in the multiplicity and size of chorionic villi, differences in the density of their stroma and the number of outer layers were employed to distinguish between early and late pregnancies.

By means of the present study we wish to call attention to a histologic method of determining the age of pregnancy early in its development, which has proved its practical worth in our laboratory since its introduction by Dr. Kornel Terplan three years ago. Based on the maturation of red blood corpuscles in the fetus, with their development from nucleated to nonnucleated forms, and a differential enumeration of these elements in chorionic capillaries, this method palpably eliminates personal factors in interpretation and furnishes results which can be expressed in quantitative terms. The *Quarterly Cumulative Index Medicus* and the monographs of Meyer [1] and Frank [2] reveal no reference to a systematic investigation identical with ours. Williams,[3] however, in a discussion of placental chronology, wrote: "It should be remembered that during the first 8 to 10 weeks of pregnancy the blood cells of the fetus are nucleated, but afterward the nuclei are lost."

PROCEDURE

One hundred consecutive specimens labeled "placental tissue" and bearing trustworthy clinical data were received following delivery, curettage, abortion or operations for tubal pregnancy. Each specimen was fixed for sixteen hours in 10 per

From the Pathological Laboratory, Buffalo General Hospital, and the University of Buffalo School of Medicine.

1. Meyer, Robert, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 7, p. 649.

2. Frank, R. T.: Gynecological and Obstetrical Pathology, ed. 2, Gynecological and Obstetrical Monographs, vol. 12, New York, D. Appleton and Company, 1931, vol. 12.

3. Williams, J. W.: Obstetrics, New York, D. Appleton and Company, 1930.

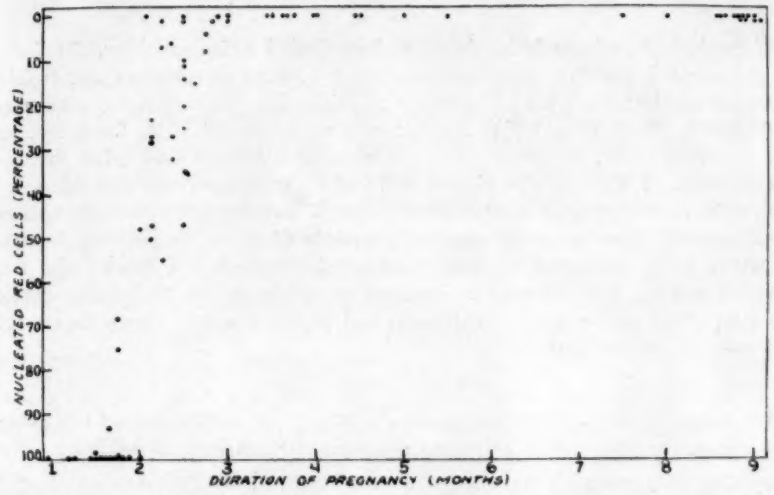

Fig. 1.—Percentage of nucleated red blood cells in the chorionic villi of seventy placentas of various ages.

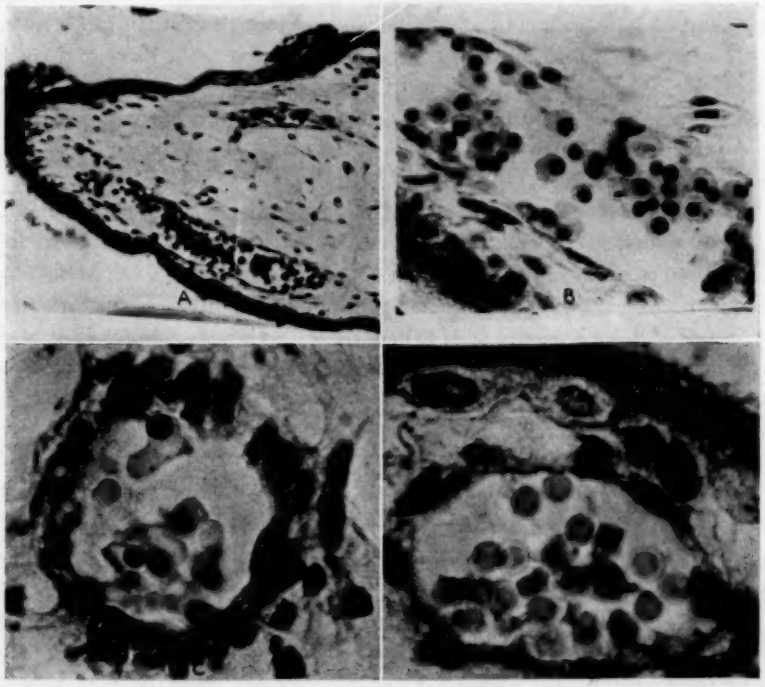

Fig. 2.—*A*, villus showing capillaries filled with nucleated red cells (low power magnification); *B*, corpuscles in a chorionic capillary in a six weeks' pregnancy (immersion in oil); *C*, corpuscles in a chorionic capillary in a two months' pregnancy (immersion in oil); *D*, corpuscles in a chorionic capillary in a pregnancy of three months or over (immersion in oil).

cent formaldehyde. After being dehydrated in alcohol and chloroform, the tissue was embedded in paraffin. Sections were cut 8 microns in thickness and stained with hematoxylin-eosin. With low power magnification, villi containing capillaries were located. Then from 100 to 200 red cells were counted while the specimens were immersed in oil, the whole process consuming not more than a few minutes for each slide. The proportion of nucleated and non-nucleated cells was calculated in percentages. In several cases differentiation of megaloblasts from normoblasts was attempted. The age of pregnancy was deduced from the patient's history, conception being postulated as having occurred seven days following the last menstrual period. Not infrequently information relative to the size of the uterine cavity, measured at the time of curettage, and to the length of the fetus offered supplementary control material.

OBSERVATIONS

Of the 100 specimens examined, 30 had to be discarded as unfavorable for study because of extreme autolysis or scarcity of villi. In the remaining 70, gradual replacement of nucleated by non-nucleated red cells took place rapidly and almost completely during the second and third months of pregnancy. The accompanying graph shows the percentage of immature red corpuscles in the 70 fragments, correlated with the respective ages of the specimens. Before the sixth week the capillaries showed 100 per cent erythroblasts. After the third month normoblasts could be found only in the ratio of 1 to several thousand mature corpuscles. Finer classification of non-nucleated forms into megaloblasts and normoblasts was possible in cases of very early pregnancy.

COMMENT

This study brings out the fact that gradual replacement of erythroblasts by mature red cells in chorionic capillaries occurs at a rate definite and constant enough to warrant its forming the basis of a histologic method of determining the age of pregnancy from placental fragments. If all the chorionic corpuscles are nucleated, the pregnancy is probably not older than two months. If more than 1 per cent are nucleated, the age is less than three months. If fewer than 1 per cent of the red cells are immature, pregnancy has passed beyond three months. Abnormal erythropoiesis constitutes the chief factor of error in this method. Otherwise, no special training is required for its use. Small fragments of tissue fixed and stained by the usual technic suffice. With practice, no more than a few minutes need be taken for calculation. Readings can be recorded as actual figures rather than as personal opinions of visual observations. As a consequence of this last feature, enumeration of chorionic red corpuscles in a fetus with normal erythropoiesis assumes a rather independent diagnostic value, especially in cases of early pregnancy in which the history is false or confusing and in which medicolegal problems are involved.

Mention must be made of several implications incidentally brought out by our study. We were early impressed by the fallibility of mea-

surements of the uterine cavity obtained by sounds, as compared with other methods of diagnosing the age of pregnancy.

Of special significance was the relation of our figures to the presumptions commonly accepted by different authors concerning the rate of disappearance of nucleated red cells, their persistence in the fetus in late pregnancy and their presence at birth. Standard textbooks state that normoblasts are found in moderate numbers in infants born at term. Further, they infer that maturation occurs gradually and over an extended period. Such views are held by many. Our observations, in addition to suggesting that the disappearance of erythroblasts takes place rapidly during two months, support the belief of Loos,[4] Hayem,[4] Lewis and Bremer [5] and Starling [6] that nucleated red cells do not occur normally in the new-born or are very rare. In smears from 13 new-born infants, Forkner [7] found nucleated red cells in only 5. From her work, Heath [8] considered low counts (less than from 1 to 2 per cent) physiologic. Counts so low would not be reflected in the total number of red cells (from 100 to 200), which we inspected. Smears from new-born infants were used to check the full term placental specimens. The same infrequency of nucleated red blood cells was noted.

Whether hematologic examination of chorionic capillaries in late pregnancy and at delivery can be used as a means of predicting and prognosticating various pathologic conditions, such as fetal dropsy, icterus gravis neonatorum, anemias of the new-born, prematurity and stillbirth (from fetal erythroblastosis), is an arresting matter for speculation.

SUMMARY

In an effort to formulate an additional histologic method of diagnosing the age of pregnancy, 70 placental fragments were examined, and differential counts of the number of nucleated and non-nucleated red cells in the chorionic capillaries at different periods of gestation were made. Replacement of nucleated by non-nucleated forms took place rapidly and almost completely during the second and third months. Therefore, if all the chorionic corpuscles are nucleated, the pregnancy is probably not older than two months. If more than 1 per cent are nucleated, the age is less than three months. If fewer than 1 per cent of the red cells are immature, pregnancy has passed beyond three months.

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4. Cited by Lippman, H. S.: Am. J. Dis. Child. **27**:473, 1924.

5. Lewis, F. T., and Bremer, J. L.: Textbook of Histology, Philadelphia, P. Blakiston's Son & Co., 1927.

6. Starling, E. H.: Principles of Human Physiology, Philadelphia, Lea & Febiger, 1926.

7. Forkner, C. E.: Bull. Johns Hopkins Hosp. **45**:75, 1929.

8. Heath, Evelyn: Bull. Buffalo Gen. Hosp. **4**:42, 1926.

SUBCUTANEOUS NODULES INDUCED BY THE INJECTION OF STREPTOCOCCUS VIRIDANS

SPECIFICITY OF THE LESION AND ORIGIN OF THE POLYBLASTS

LYDIA LUX

MINNEAPOLIS

In a series of reports, Clawson has described the nodule associated with acute rheumatic fever. In 1928 he [1] gave a general description of the inflammatory reaction involved. He described the nodule as a "localized area of inflammation, mostly proliferative in character, found in the loose connective tissue beneath the skin in a limited number of cases of acute rheumatic fever." These nodules, he stated, appear to be similar in morphology to those produced experimentally in rabbits by the injection of Streptococcus viridans. In 1929 Clawson [2] commented on the cellular morphology of the nodule and pointed out that the rheumatic nodules should not be regarded as a specific anatomic lesion in the same sense as the tuberculous or syphilitic lesion. In 1930 he [3] described the reaction in normal, immune and hypersensitive animals and concluded that the reaction in hypersensitive animals differed in no way qualitatively from that in normal and immune animals. This view is in accord with that of Maximow. In his work on mesenchymal reactions Maximow [4] said regarding allergic reactions, "As far as one can judge by the still modest accumulations of facts available at present, the differences, as compared with the histogenesis of common inflammation, are quantitative, rather than qualitative." Von Möllendorff [5] agreed that the reaction in a hypersensitive animal differs from that in a normal animal only in degree.

The question of the origin of the free nongranular phagocytic cells in the field of reaction of these lesions is of great importance in this problem. Clawson [3] stated that they are both hematogenous and histogenous in origin. McEwen [6] described a cell derived from the "undifferentiated mesenchyme" of the loose connective tissue, which he thinks

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1. Clawson, B. J.: Am. J. Path. **4**:565, 1928.
2. Clawson, B. J.: Arch. Path. **8**:654, 1929.
3. Clawson, B. J.: Arch. Path. **9**:1141, 1930.
4. Maximow, A.: Arch. Path. **4**:557, 1927.
5. von Möllendorff, W.: Ztschr. f. Zellforsch. u. mikr. Anat. **6**:61, 1927.
6. McEwen, C.: J. Exper. Med. **55**:745, 1932.

is specific for the lesion. This cell will be discussed later. Both Clawson and McEwen referred in detail to conclusions of various earlier workers regarding the origin of these cells; hence it is unnecessary to consider them here.

In this investigation, questions concerning the specificity of the lesion, the behavior of the fibroblasts and the origin of the free phagocytic cells were given special consideration.

MATERIAL AND METHODS

The material consisted of nodules removed from hypersensitive adult rabbits that had been killed at intervals of six and twelve hours, one, two, three, four, five, seven and nine days after they had been given multiple injections of Streptococcus viridans.

These animals had been made hypersensitive by a subcutaneous injection of about 5 cc. of a heavy suspension of melted agar and streptococci. A large abscess developed at the point of injection. Twelve days later, at the time which had been previously determined to be best for the formation of subcutaneous nodules, the multiple injections mentioned were made into the back of the animals on the side opposite the one with the large abscess.

The organisms were cultured in a broth tube for forty-eight hours, allowed to settle to the bottom of the tube and then decanted. A suspension of the organisms was then made up with 10 cc. of physiologic solution of sodium chloride, and 0.1 cc. of this suspension was used for each of the subcutaneous injections. This dosage proved to be the minimum amount that would produce nodules in normal animals, as previously determined by Clawson.[8]

Several nodules were removed from each animal. A middorsal incision was made, the skin was laid back, and the nodules were found in the tissue adhering to the skin. These nodules appeared as white areas, variable in size and not always easily distinguished from the surrounding tissue.

The removed nodules were fixed for six hours in Zenker's fluid to which a dilute solution of formaldehyde had been added and were washed in running water for twenty-four hours. The paraffin method of embedding was used, and serial sections were made in some instances. Hematoxylin and eosin, methyl green and pyronine, and Maximow's hematoxylin-eosin-azure stains were used on many of the sections, while Dominici's stain was used as a routine procedure.

MICROSCOPIC STUDY

Low Power Magnification.—The cellular infiltration was diffuse up to the one day stage, while the later stages showed either single or multiple formation of abscesses. The one day stage showed a slight amount of degeneration, while in the four day stage there was an abscess with a central area of necrosis. Abscesses with necrotic centers were present in all of the following stages, but none of these showed evidence of hyalinization.

Edema was marked in the early stages, but after five days little was noted, and it was completely absent in the nine day stage.

Hemorrhage appeared irregularly throughout the series, but it was most marked in the two day stage.

Increased vascularity was noted in all stages, the blood vessels appearing dilated. Migration of cells was more pronounced in the early stages of the reaction than

after the four day stage. The walls of the blood vessels were thickened in many instances but never to the extent of occlusion of the lumens of the vessels.

The fourth day was the earliest stage in which there was definite orientation of fibroblasts suggesting formation of capsules. In the five day stage the number of fibroblasts had increased and the capsule had taken a more definite form. In the last two stages the abscess was completely surrounded by a definite layer of fibroblasts. In all stages there was an increased vascularity in the areas of fibroblastic proliferation.

Throughout this material there could be noted special areas characterized by marked vascularity. Such areas had no obvious relation to the nodules, but the thickening of the walls of the vessels indicated that they were involved in the reaction. In some instances there was marked perivascular lymphocytic infiltration.

High Power Magnification.—Edema was one of the earliest responses following the injection of the organisms. It increased progressively in the later stages, reaching a maximum about the fifth day, after which it became less marked. None was noted after the seven day stage.

In all stages there was considerable hemorrhage into the area of reaction. It was most marked, however, in the two day stage.

Cellular infiltration was also an early feature of the reaction. Many polymorphonuclear leukocytes and lymphocytes and a few monocytoid cells and eosinophils were present in the early stages, but the polymorphonuclear leukocyte was the predominating cell type. There was some degeneration of polymorphonuclear leukocytes in the six hour stage, and this increased in degree as the reaction advanced. Formation of abscesses was noted as early as the one day stage, the abscesses being multiple in many instances. After three days these abscesses were found to have necrotic centers, but there was no evidence of hyalinization. Degeneration of cells, except within the area of the abscess, was no longer a prominent feature after the fifth day.

Comparatively few lymphocytes were present in the six hour stage, but they increased in number in the later stages. Beginning with the two day stage, they showed a tendency to collect around the blood vessels.

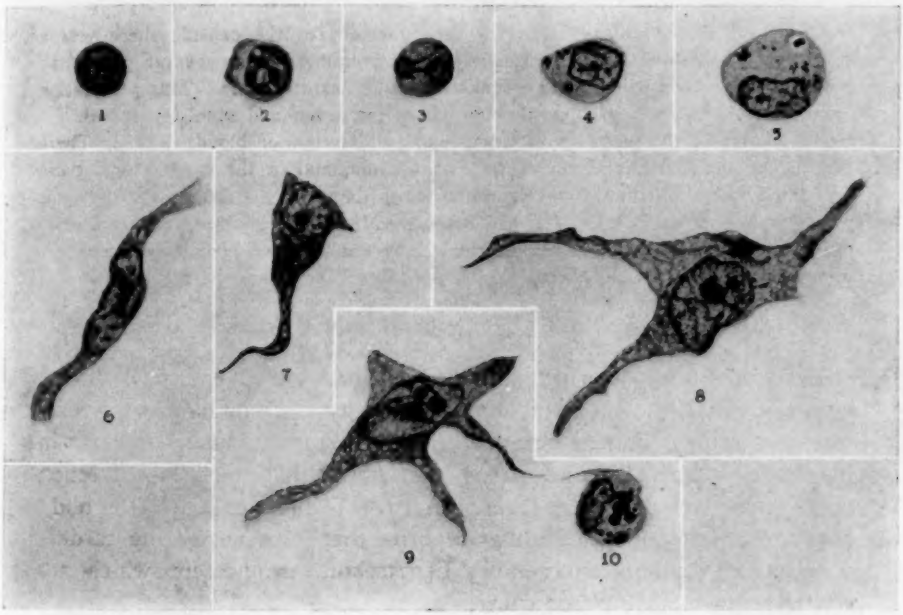
Migration of leukocytes became less prominent as the reaction advanced, but even in the latest stages studied it could be noted.

Few polyblasts were present in the six and twelve hour stages, and only an occasional one was actively phagocytic. After the twelve hour stage there was a marked increase in the number of phagocytic cells, and some were still present in the nine day stage. In the one and two day stages many of the lymphocytes had increased in size, and transitional forms from lymphocyte to polyblast were a conspicuous feature. Even in one microscopic field one could trace all the stages, from small lymphocytes, through hypertrophic intermediate stages, to active phagocytic polyblasts, as is shown in the illustration. The lymphocytes, such as cells 1 and 2, were found in great numbers in some areas. From the transitional forms one could assume that as the lymphocytes enlarged, their cytoplasm became less basophilic, and in many instances vacuolated. The coarse nucleus became less dense in structure and assumed an irregular or indented form. This series of changes is shown in cells 1 to 5. However, many cells retained their original size and were less basophilic but contained some engulfed material. Many of the large phagocytes were loaded with granules from polymorphonuclear leukocytes, nuclear remnants from degenerating leukocytes and erythrocytes.

Among the fibroblasts found in the early stages many were large and swollen in appearance. The outline of the cell was indefinite, and processes were no

longer evident. The cytoplasm was pale and vacuolated, giving the cell a spongy appearance. In many instances the boundary of the cell could not be made out, and the cytoplasm appeared scant or even completely lacking. The nucleus was large and pale. Nucleoli were always present in varying numbers, but usually two were noted. The remainder of the fibroblasts varied widely in appearance, some being practically normal spindle cells while others were quite rounded, with deep basophilic cytoplasm and irregular cell outlines.

After the one day stage the fibroblasts increased in number as the reaction advanced. Although there was some suggestion of concentric orientation of fibroblasts in the three day stage, the fourth day was the first in which there was definite formation of a capsule. In general, in the later stages there was an



The illustration was drawn from sections stained with Dominici's eosin-orange-G-toluidine blue. Cells 1 to 5 are from the subcutaneous tissue of adult rabbits two days after injection. They show the transition of lymphocyte to polyblast. Cells 1 and 2 are small lymphocytes; cells 3 to 5, polyblasts of lymphocytic origin. A single field is represented. Cells 6 to 10 are from subcutaneous tissue of adult rabbits five days after injection; cell 6, a fibroblast drawn from the periphery of the newly forming capsule; cell 7, a fibroblast from a zone between the capsule and a nearby vascular area; cells 8 and 9, fibroblasts from a field close to a vascular area near the capsule; cell 10, a polyblast from this same field.

increase in the thickness of the capsule accompanied by a marked increase in vascularity.

Beginning with the one day stage, where fibroblasts started to increase in number, there was an increase in the variety of types of fibroblasts seen, which reached a maximum on the fifth day. Cells 6 to 9 were drawn from this stage to show the extreme variation in form. In general, the small forms had a deeply

basophilic cytoplasm; some were almost round. They assumed the flattened form as one approached the area in which the capsule was being laid down. Cells 6 to 9 illustrate some of the more extreme forms. These resembled in certain ways the damaged cells described in the early stages. They had a pale vacuolated cytoplasm, but they were more branched and had a more definite cell boundary than the damaged cells. Furthermore, the nucleus was not as pale. It was not possible to follow the damaged cells through the three and four day stages and to establish with certainty their relation with the extreme forms seen in the fifth day.

The fibroblasts at no time proved to be phagocytic, though they were found in areas where degenerating leukocytes and many active phagocytic polyblasts were present, as is shown by cells 9 and 10 which were in the relation depicted in the illustration.

The capsule completely surrounded the abscess after the four day stage. At the junction of the abscess with the inner surface of the capsule there was a considerable number of phagocytic polyblasts present, and at several points the fibroblasts were beginning to penetrate the central necrotic mass. This penetration by the fibroblasts was particularly marked in the seven and nine day stages.

In all stages of the reaction there was a dilatation of blood vessels. There was also a marked thickening of the endothelium, and in the early stages there was some suggestion that free cells were being liberated into the lumen. In some places it appeared that the vessel had become entirely disorganized, leaving a mass of fibroblast-like cells, the exact origin of any one of which could not be determined. This was especially noted in the two, three and four day stages.

COMMENT

The specificity of rheumatic nodules has been a much discussed question. In 1904 Aschoff [7] described this type of inflammatory reaction as specific for acute rheumatic fever. Sometime later Coombs,[8] in his work on rheumatic infections, also stated that this type of lesion was specific for rheumatic fever. In 1914 Thalhimer and Rothschild [9] confirmed that opinion when they reported that in rheumatic myocarditis foci termed "submiliary nodules of Aschoff are present which are characteristic of rheumatic infections."

Contrary to this point of view, Clawson [2] in his report on the Aschoff nodule found that rheumatic nodules cannot be considered as characteristic of rheumatic fever. He stated that they are more commonly found in association with acute rheumatic fever, but that they are also found in cases of nonrheumatic infectious diseases. He did not consider the histologic picture distinctive for this type of lesion.

It has already been stated that Clawson [1] concluded that the experimental nodules were similar in histology to the nodules found in subcutaneous tissues in cases of acute rheumatic fever.

In the material studied here, the early stage was essentially exudative with a subsequent breakdown of the central part of the area involved.

7. Aschoff, L.: Verhandl. d. deutsch. path. Gesellsch. **8**:46, 1904.
8. Coombs, C.: Brit. M. J. **2**:1513, 1907.
9. Thalhimer, W., and Rothschild, M. A.: J. Exper. Med. **19**:417, 1914.

The abscess was then surrounded by a reaction field occupied by free ameboid phagocytic cells of various sizes. In the later stages emigration of hematogenous cells was still taking place to some extent. The cells of the lymphoid series were becoming more numerous in relation to the granulocytes.

The fibroblasts were involved from the start. They soon lost their processes, increased in size, and in general showed changes that appeared to be degenerative. They began to increase in number after the one day stage, and this increase was particularly marked on the third day when they began to participate in the formation of a capsule. From this point on the picture was one of fibroblastic proliferation. Obviously there was overlapping of these processes.

This general description as well as the detailed microscopic study on which it is based shows that the course of events here corresponded closely with that well established for inflammatory reactions in general. These observations therefore in no way support the contention that the lesion shows a characteristic histologic picture.

ORIGIN OF FREE NONGRANULAR PHAGOCYTIC CELLS

Clawson [3] found evidence that the phagocytic cells in these nodules were both hematogenous and histogenous.

McEwen [6] studied the large irregularly shaped cells found in scrapings of subcutaneous nodules removed from patients with rheumatic fever. From the results of supravital staining he concluded that these cells took origin from the undifferentiated mesenchyme of the loose connective tissue. He based his conclusion on the fact that the "granuloma cells" did not take up neutral red in supravitally stained preparations, whereas other cells took up various amounts of dye according to their nature. As additional evidence that these cells are undifferentiated he points out that they exhibit developmental tendencies; that is, a limited number of them take up particles of carbon. He believes that certain transitional forms indicate that they may be transformed into fibrocytes.

Regarding the origin of free nongranular cells in nonspecific inflammatory processes, there are two schools of thought. As early as 1905 Maximow [10] described septic and aseptic inflammatory reactions and stated that the origin of polyblasts from hematogenous cells was evident, but that fibroblasts contributed in no way to the phagocytic cells present. The fibroblasts in the immediate field he described as showing degenerative changes with the nucleus shrunken in appearance and a much vacuolated cytoplasm. The fibroblasts more distant from the field of reaction were forced apart but not altered.

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10. Maximow, A.: Beitr. z. path. Anat. u. z. allg. Path. **38**:301, 1905.

In 1927, Maximow [4] discussed in detail the cells involved in inflammatory reactions. He stated that the polyblasts originated from lymphocytes and monocytes and to a lesser degree from the histiocytes of the connective tissue. He found no evidence for the origin of ameboid phagocytic cells from endothelium of blood vessels and cited the work of Lang [11] and Stilwell [12] as corroborating this view. He claimed that the endothelium merely formed capillary sprouts and that in inflammation and culture of tissue some of its cells became fibroblasts. In all of his work, Maximow found no evidence of fibroblasts becoming phagocytic polyblasts. He noted,[13] however, in his cultures of lymph nodes inoculated with tubercle bacilli, an "embryonic transformation" of the fibroblasts which he considered as a "specific" reaction of these cells to the tubercle bacillus.

Two years later when Maximow [14] repeated the work of von Möllendorff with subcutaneous injections of trypan blue, he again found that most of the polyblasts in the field of reaction took origin from hematogenous lymphocytes and monocytes, and that after two days phagocytes derived from lymphocytes could not be distinguished from those that originated from monocytes.

In 1925 Maximow [15] postulated the "undifferentiated mesenchyme cells" of connective tissue, which morphologically appear to be fibroblasts but differ physiologically, since they are presumed to have practically unlimited developmental potencies. The undifferentiated mesenchyme cells in contrast to histiocytes do not store colloidal dyes. These cells are found particularly along blood vessels.

Bloom [16] injected a suspension of Bacterium monocytogenes into a rabbit subcutaneously. An abscess developed which was similar to reactions due to other inflammatory stimuli. He noted that the phagocytes of the abscess were practically exclusively of hematogenous origin. He stated that "in none of these inflamed tissues was there any evidence in favor of the special leukocytes and exudative mononuclear phagocytes developing either from fibroblasts or from vascular endothelium."

Michels and Globus,[17] in their descriptions of infiltrations of round cells in the central nervous system, stated that in dementia paralytica and in encephalitis the vast majority of exudate cells originated from emigrated lymphocytes and monocytes and that a small number were "homoplastic derivatives of preexistent or previously extravasated

11. Lang, F.: Arch. Path. **1**:41, 1926.
12. Stilwell, F.: Folia haemat. **33**:81, 1926.
13. Maximow, A.: J. Infect. Dis. **34**:549, 1924.
14. Maximow, A.: Beitr. z. path. Anat. u. z. allg. Path. **82**:1, 1929.
15. Maximow, A.: J. Infect. Dis. **37**:418, 1925.
16. Bloom, W.: Arch. Path. **6**:995, 1928.
17. Michels and Globus: Arch. Path. **4**:692, 1927; **8**:371, 1929.

lymphoid cells." Formation of exudate cells from the so-called adventitial cells of Marchand or any other fixed connective tissue cells was not noted in their work. In all instances, even when perivascular infiltration was maximal and connective tissue was hypertrophic, they found no rounding of fibroblasts and no amitosis.

The point of special interest in these contributions is the fact that they present no evidence in favor of the origin of polyblasts from fibroblasts.

On the other side of this question we find that as early as 1911, Downey [18] called attention to the participation of fibroblasts in the formation of plasma cells. In his work [19] on the structure and origin of lymph sinuses of mammalian lymph nodes he pointed out that fibroblasts ordinarily reacted slowly to vital dyes and foreign substances. However, fibroblasts of the omentum, which formed an exception to this rule, reacted vigorously to vital dyes and foreign substances and readily became free cells which could differentiate into various types of lymphoid cells.

Lindsey,[20] under the direction of Downey, worked on reactions of the subcutaneous tissue to experimental tuberculosis in the guinea-pig. She regarded the fibroblasts as "relatively undifferentiated cells closely related to mesenchyme." She claimed that these cells were transformed into exudate cells, including clasmatocytes, monocytes, lymphocytes, polyblasts and epithelioid cells. She found monocytoid cells originating locally from fibroblasts, and these represented intermediate stages in the formation of epithelioid cells. Similar investigations were continued by Downey's student, Ekola,[21] who worked on reactions of subcutaneous tissue to foreign substances. She found transitional stages on which she based the conclusion that fibroblasts gave rise to polyblasts and clasmatocytes. She also found evidence for the origin of polyblasts clasmatocytes and lymphocytes.

Watson,[22] also working under Downey's direction, described a case of histoplasmosis in which he made special reference to the origin of phagocytic cells. In the liver these cells took origin from small lymphocytes, reticulo-endothelial cells of the liver sinusoids, and rarely from fibroblasts. He found that the macrophages in the lymph nodes were from two sources, the lymphocytes and reticular cells, while those in the lung came from lymphocytes, alveolar epithelial cells and adventitial histiocytes from capillaries of the lung.

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18. Downey, H.: Folia haemat. Arch. **11**:271, 1911.
19. Downey, H.: Haematologica **3**:431, 1922.
20. Lindsey, M. L.: Am. Rev. Tuberc. **19**:615, 1929.
21. Ekola, M. W.: Folia haemat. **43**:4, 1931.
22. Watson, C. J.: Folia haemat. **37**:70, 1928.

Any discussion of the origin of macrophages from fibroblasts must take into consideration the opinions of von Möllendorff.[23] From his investigation of inflammatory reactions induced by subcutaneous injections of trypan blue in mice and rabbits, he concluded that polyblasts were only in part hematogenous. He maintained that fibroblasts played an important rôle in the production of phagocytes and granulocytes in inflammation. The fibrocytes of loose connective tissue he considered as part of a diffuse syncytium which when stimulated gave rise to many large ameboid mononuclear cells. He regarded the adventitial cells of Marchand as a stimulated part of the net in the region of the vessels. The first changes noted in his experiments were granulation and vacuolation of some of the fibroblasts with a contraction of the cell and nucleus and a complete separation from the net as free cells. These free cells, for the most part, even as early as twenty-eight hours after injection, became round cells with polymorphous nuclei and then degenerated.

One year later, while working with normal and hypersensitive animals, von Möllendorff [24] injected serum subcutaneously and found that after only a few hours one could distinguish transitional stages between fibroblasts and large basophilic round cells that finally became granulocytes and then degenerated.

Maximow [14] in repeating the work of von Möllendorff found no proof for the origin of free phagocytic cells from fibroblasts.

Lindsey [20] agreed in part with von Möllendorff when she stated that fibroblasts of the subcutaneous tissue into which tubercle bacilli were injected gave rise to exudate cells. However, she found no evidence for the formation of polymorphonuclear leukocytes from fibroblasts. The nuclei of many polyblasts became lobulated, and these, she claimed, looked like pyknotic polymorphonuclears, the granules of which had disappeared.

Ekola [21] also concluded that fibroblasts gave rise to polyblasts and clasmatocytes. In many instances the intermediate forms were vacuolated and were active phagocytic cells. However, she found no evidence that granulocytes developed from connective tissue cells as was claimed by von Möllendorff.

Bloom,[25] in his excellent summary on cellular relationships in general, commented on the origin of macrophages from fibroblasts. While he stated that he does not think that fibroblasts are an important source of macrophages in inflammatory reactions in general, he did not deny the possibility that the change can take place.

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23. von Möllendorff, W., and von Möllendorff, M.: Ztschr. f. Zellforsch. u. mikr. Anat. **3**:503, 1926.

24. von Möllendorff, W.: München. med. Wchnschr. **74**:135, 1927.

25. Bloom, W.: Arch. f. exper. Zellforsch. **11**:145, 1931.

There are a number of reports from workers on tissue cultures, beginning with the report of Carrel [26] in which he stated that twice in fourteen years he observed in the periphery of his cultures of embryonic heart muscle a spontaneous change of fibroblasts to free ameboid cells.

Fischer,[27] in 1926, in his cultures derived from chick heart which he regarded as pure fibroblasts, found that these fibroblasts became ameboid macrophages that differed from fibroblasts morphologically and physiologically. These cells were different from those found in dying and degenerating cultures.

Parker [28] found a transformation from fibroblast to macrophage in his culture of fibroblasts derived from heart and skeletal muscle. Only a limited number of his cultures showed this transformation, which seemed to take place at some critical period in the life of the culture in which degeneration was taking place at a relatively slow rate. He quoted Ephrussi and Hugues [29] as having noted this same transformation.

The material studied in this investigation supports the contention that the fibroblasts in no way contribute to the formation of phagocytic cells. The change in the fibroblasts as evidenced early was essentially a shortening or loss of processes. The outline of the cell was irregular and poorly defined, and the cytoplasm was pale and vacuolated. In many instances the cytoplasm was scant and at times even completely lacking. The nuclei were large and vesicular and were often found in groups when no outline of cells was evident. At no time were these cells phagocytic, nor could intermediate forms be found to suggest any relation to the phagocytic polyblasts present in the material.

When fibroblastic proliferation began the picture changed and there was a sudden marked increase in fibroblasts. At no time was there a great number of mitotic figures or evidence of amitosis. There was some suggestion that polyblasts were being transformed into fibroblasts, but no satisfactory series of intermediate stages could be found.

The origin of polyblasts from hematogenous cells was evident. Early in the reaction transitional stages between the various lymphoid cells which showed practically no phagocytic tendencies and polyblastic phagocytes of various sizes could be readily followed, as is indicated by cells 1 to 5 in the illustration. The transitional forms show a cytoplasm that is less basophilic and more vacuolated, while the nucleus is irregular in form and of a less dense structure.

The picture here is identical with that described by the group which derives the polyblasts from hematogenous cells. That fibroblasts undergo marked changes is obvious, but there is nothing in this material

26. Carrel, A., and Ebeling, A. H.: J. Exper. Med. **44**:261, 1926.
27. Fischer, A.: Arch. f. exper. Zellforsch. **3**:345, 1926.
28. Parker, R.: J. Exper. Med. **55**:713, 1932.
29. Ephrussi, B., and Hugues, Y.: Compt. rend. Soc. de biol. **105**:697, 1930.

to justify the conclusion that these changes should be interpreted as leading to the formation of phagocytic cells.

Special note should be taken of the work of Lindsey and Ekola in their confirmation of von Möllendorff on this point. And the opinions of those working with culture of tissue, in which less complex conditions render errors of interpretation less probable, have also been cited in favor of the fibroblastic origin of phagocytes.

While the particular materials and methods used in this investigation entirely failed to show the transformation of fibroblasts into phagocytes, I am willing to admit that under other circumstances this transformation may take place.

CONCLUSIONS

The nodules studied revealed a nonspecific inflammatory reaction.

The lymphoid cells of the exudate constitute the chief source of phagocytic cells seen in these lesions.

There is no evidence that fibroblasts are transformed into phagocytic cells.

General Review

ORIGIN AND NATURE OF THE LESION OF SYMPATHETIC OPHTHALMIA

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BROOKLYN

Even the laity is aware of the fact that a person sustaining an injury to one eye is liable to lose the vision in the uninjured eye by virtue of some mysterious process called sympathy or sympathetic disease. Many physicians, while generally conversant with the clinical aspects of this phenomenon, are perhaps as unfamiliar as are the laymen with the pathologic process involved. It is with this thought in mind that I am presenting a review of the knowledge of this unusual disease which has furnished the basis for an enormous volume of philosophic discussion and intriguing although not conclusive research.

THE TYPICAL LESION

A small percentage of enucleated eyes show, on histologic examination, a picture which has come to be looked on as practically pathognomonic of sympathetic ophthalmia.

In sections of such eyes one finds an inflammatory lesion of the granulomatous type involving chiefly the uveal tissue with little involvement of other structures. There is rather diffuse or focal round cell infiltration of the iris, ciliary body and choroid, the degree of infiltration being variable in the different structures but tending to involve the entire uvea. Among the round cells are found nests of closely packed epithelioid cells which frequently contain giant cells of the Langhans type. The epithelioid collections closely resemble epithelioid tubercles except for the absence of caseation.

A striking characteristic is the constancy with which the process is confined to the uvea. Invasion of the sclera is limited to the region of the emissaria, where mantles of round or epithelioid cells may be found surrounding the perforating vessels and nerves. Occasionally there is extension into the optic nerve head, while only rarely is there any invasion of the retina.

Omitting, for the moment, consideration of minor features, a picture such as I have described could be considered fairly diagnostic of

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this disease entity. If, in addition, it were known that the sections were from an eye which had sustained a perforating wound in the ciliary region and that, prior to enucleation, the other (uninjured) eye had begun to show signs of inflammation, a diagnosis of sympathetic ophthalmia could be made with certainty.

DEFINITIONS

Sympathetic Ophthalmia.—Prior to the anatomic studies of Schirmer [1] and Fuchs [2] and his school, the term sympathetic ophthalmia was understood to refer only to the disease in the uninjured eye. The lesion in the injured eye was thought to be an ordinary traumatic endophthalmitis which in some way was communicated to the opposite eye. These investigators showed that an anatomically well defined and apparently specific form of uveitis could be found in the injured eye as well as in the eye suffering in sympathy. This process was designated by Fuchs as sympathetic inflammation.

The tendency, still evident in the literature, to designate as sympathetic ophthalmia only the process in the eye which is secondarily involved is perhaps in part reminiscent of the older concept and in part due to the lexicologic force of the word sympathetic. From a pathologist's point of view, it seems advisable to employ the term "sympathetic ophthalmia" (in the sense of Fuch's sympathetic inflammation) to indicate the characteristic lesion of the disease and not the extent of involvement of the susceptible (uveal) tissue.

With this preamble I would broadly define sympathetic ophthalmia as a granulomatous lesion of the eye characterized chiefly by its tendency to involve the uveal tissue of both eyes.

Exciting [3] *Eye.*—Assuming for the present that the disease begins first in one eye, which in most instances has sustained a perforating wound (nonsurgical or surgical) in the ciliary region, this eye is variously described as the "primary" eye, the "sympathogenic eye" or, as I shall refer to it, the exciting eye.

Sympathizing [4] *Eye.*—The eye subsequently involved, sometimes called the "secondary" eye, will be referred to as the sympathizing eye.

Such terms as sympathetic iritis, sympathetic choroiditis and sympathetic scleritis, frequently encountered in the literature, are employed not to indicate separate disease entities but to designate the involvement

1. Schirmer, O.: (*a*) Arch. f. Ophth. **38**:4, 1892; (*b*) in Graefe-Saemisch: Handbuch der gesamten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1900, vol. 6, p. 2.

2. Fuchs, E.: (*a*) Arch. f. Ophth. **61**:365, 1905; (*b*) **70**:465, 1909.

3. Sympathisierende, sympathisant, simpatizzante.

4. Sympathisierte, sympathisé, simpatizzato.

of the various portions of the eye in the disease process. When the process is almost exclusively limited to, or unusually prominent in, one or another of these structures, such a term is more accurately descriptive than the general term, sympathetic ophthalmia.

HISTORICAL REVIEW

Concerning the early history of sympathetic ophthalmia, one might best refer to Parsons'[5] "Pathology of the Eye," from which, because of its relative inaccessibility, the following passages are quoted:

> The earliest reference to sympathetic ophthalmia is found in the oldest German text-book of ophthalmology by Bartisch (1583), who remarks that in cases of injury to one eye "the other good eye is besides also in great danger." Le Dran (1741) says: Si comme aux abscés qui se font ailleurs on attend que le pus soit fait le malade pourra perdre la vue par l'inflammation qui se communiquera à l'autre oeil le long du nerf optique." Two undoubted cases are recorded by Demours (1818). Wardrop (1819) reported a case of sympathetic iritis briefly, and mentioned that veterinary surgeons had noticed destruction of the second eye in horses, and that it might be avoided by destruction of the first eye by lime (cf. Barton, Crompton). Lawrence (1833) recorded several cases. The true history of sympathetic ophthalmia may be said, however, really to have commenced with the masterly description and imaginative insight of William Mackenzie (1835).
>
> Sympathetic ophthalmia was first mentioned under this designation in Germany by v. Ammon (1838). Neither he nor Himly (1843) appear [sic] to have been conversant with Mackenzie's work; his name is not mentioned and the descriptions are much less accurate and complete.
>
> The next notable contribution to our knowledge of the disease was made by Augustin Prichard (1851), of Bristol, who first proved the efficacy of excision of the exciting eye. This treatment was received with distrust, even by v. Graefe, who preferred iridectomy, and finding this useless, resorted to the production of panophthalmitis by passing a thread through the eye; he mentions optico-ciliary neurotomy, but does not appear to have employed it. v. Graefe later recognized the value of excision of the exciting eye, and advanced the opinion (1866) that inflammation of the uveal tract was sine qua non to sympathetic inflammation. At the Ophthalmological Congress at Heidelberg in 1863 George Critchett contributed important additions to our knowledge of the clinical picture of the disease, v. Graefe distinguished between the more malign (plastic) and less grave (serous) forms of sympathetic iritis, and Donders adduced evidence of a sympathetic neurosis which is promptly cured by excision of the exciting eye.

The more recent history of the disease concerns largely the development of modern concepts of the nature of the pathologic process and investigations into its etiology and pathogenesis. These will be discussed later.

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5. Parsons, J. H.: The Pathology of the Eye, New York, G. P. Putnam's Sons, 1908.

LESIONS THAT MAY GIVE RISE TO SYMPATHETIC OPHTHALMIA

Most cases of sympathetic ophthalmia occur following traumatic perforating wounds in the ciliary region, which, in this sense, has become known as the dangerous zone. Less frequently the disease develops following operative procedures such as iridectomy or cataract extraction. It is usually noted that prompt and uneventful healing of the wounds has been prevented by complications such as traumatic cyclitis or incarceration of uveal tissue or lens capsule between the edges of the wound. The fact that wounds in the ciliary region are prone to such complications may account for the peculiar significance of the location of wounds (surgical or nonsurgical) in this regard.

Frankly infected wounds which lead to purulent endophthalmitis or panophthalmitis are unlikely to be followed by sympathetic ophthalmia, a fact for which no satisfactory explanation has been advanced. Occasional instances of sympathetic ophthalmia following suppurative lesions were cited from the literature by Schirmer, Peters and others and were referred to in an article by Lamb [6] in which he recorded a case of this kind.

The disease rarely follows perforating corneal ulcer, perhaps for the reason that purulent panophthalmitis is the common sequela of such a lesion.

There remains a small but important group of cases in which sympathetic ophthalmia has been reported as following nonperforating traumatic lesions, or intra-ocular tumors (usually melanomas) with or without perforation of the globe. They have given rise to a great deal of discussion, and the decisions to accept or reject individual cases in the group as instances of sympathetic ophthalmia seem to depend in part on the leanings of the reviewers with regard to the nature of the immediate causative agent and its mode of entrance into the eye. Parsons [5] suggested that "a minute wound of the conjunctiva or an abrasion through which exogenous infection might take place most probably explains the few doubtful cases [of subconjunctival rupture of the globe] in which sympathetic ophthalmia may have occurred."

Lamb,[7] in 1932, reported what seems to be an undoubtable instance of sympathetic ophthalmia following a nonperforating injury. The cornea of one eye had been slightly abraded by the blow of a stick, but no deep wound could be found. The second eye became inflamed ten weeks after the injury and, in spite of enucleation of the injured

6. Lamb, H. D.: Tr. Am. Ophth. Soc. **29**:288, 1931.
7. Lamb, D. H.: Arch. Ophth. **7**:97, 1932.

eye, it became blind and shrunken. The diagnosis was substantiated by histologic study of the enucleated (injured) eye. Lamb reviews cases of this nature reported by Kitamura, Botteri, Meller, Weigelin and Guillery, in each of which, in his opinion, there had been either a possibility of doubt as to the correctness of the diagnosis or some complicating factor such as operative intervention.

A similar case reported by Delaney,[8] in 1931, presented a typical clinical picture of sympathetic ophthalmia developing nine months after injury to one eye by a snowball. The enucleated injured eye failed, however, to show the typical histologic features of the disease, a fact which by no means disproves the authenticity of the case, as will be explained subsequently.

Leber and Krahnstöver [9] considered there was not sufficient evidence to show that sympathetic ophthalmia is ever set up by sarcoma of the choroid, though it might follow perforation of the globe through operative intervention.

Mention is usually made of extensive necrosis of the tumor tissue in these cases with the implication that it is the necrosis which has some causal relationship to the sympathetic lesion. Lamb,[6] in reporting a case of this type, refers to similar cases recorded by Fuchs, Meller and Reis.

The status of these cases will likely remain problematic until the *causa causans* of sympathetic ophthalmia is definitely proved.

The time interval between injury of the one eye and the appearance of signs and symptoms of a sympathizing inflammatory process in the other eye is extremely variable. The shortest interval is fourteen days. More often it is from four to twelve weeks, after which time the likelihood of development of the disease becomes progressively less. The longest interval recorded is forty-eight years (Smith [10]).

According to Parsons,[5] in nearly all cases in which the interval has been long the injured eye has become irritable and inflamed shortly before the onset of the sympathizing process in the other eye. "This may be spontaneous or due to trauma, often scarcely appreciable." Conversely, as stated by Smith, "when an injured eye has been free from inflammatory reaction for months or years, the subsequent appearance of inflammation in the second eye without a history of flare-ups or attacks of pain in the injured eye should be regarded as an independent condition probably of constitutional origin and therefore not directly related to sympathetic ophthalmia."

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8. Delaney, J. H.: Arch. Ophth. **5**:781, 1931.
9. Leber, T., and Krahnstöver, A.: Arch. f. Ophth. **45**:164, 1898.
10. Smith, J. W.: Arch. Ophth. **2**:169, 1929.

The frequent finding of bone in the choroid or in cyclitic membranes of shrunken exciting eyes is regarded as a sequela of phthisis bulbi and not of particular significance in sympathetic ophthalmia.

Obviously such data as the time of injury of one eye and the time of appearance of inflammation in the other eye furnish no indication of the time of onset of the specific disease in the exciting eye, and no other criteria are available by which this can be accurately determined. The specific process is always more or less completely obscured from clinical observation by the direct results of trauma or by an associated traumatic endophthalmitis. Similarly, the histologic features of an early sympathetic ophthalmia in the exciting eye may either be masked by nonspecific changes or be unrecognized because of the unfamiliarity with the earliest phases of the process.

In a clinically suggestive case, in which a traumatized eye has been enucleated as a prophylactic measure, the earliest histologic manifestations of sympathetic ophthalmia may indeed be present but not recognizable as such. Conversely, a histologically suggestive picture in an enucleated eye cannot establish the diagnosis in the absence of a sufficiently characteristic clinical history. The diagnosis in either instance is only presumptive.

The rate of development of the process in the exciting eye is evidently extremely variable. In a case reported by Kümmell [11] there were found only isolated lymphocytic foci in spite of the fact that the disease in the sympathizing eye had continued for a year. Ginsberg [12] suggested that in such a case "one is to assume that the process is in the act of retrogression." It is not uncommon, on the other hand, to find a well developed characteristic picture a few weeks after injury, as in one of my cases in which enucleation followed immediately on the onset of signs of involvement of the other eye. In this instance it seems evident that the granulomatous lesion in the exciting eye must have developed rapidly and anticipated, at least by several days, the onset of the process in the sympathizing eye.

HISTOLOGY

The histologic picture of sympathetic ophthalmia as seen in the exciting eye is always more or less complicated by the effects of injury per se or by reaction to a resulting nonspecific infection. Such exudative and reparative processes as might follow any perforating wound, and

11. Kümmell, R.: Arch. f. Augenh. **86**:143, 1920.

12. Ginsberg, Sigmund, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 2, pt. 1.

particularly plastic exudation, are not, according to Fuchs,[2a] of the nature of sympathetic ophthalmia. This view is in opposition to the earlier views of Schirmer and his pupil Ruge,[13] who believed that plastic exudate is a characteristic, but not essential, feature of sympathetic ophthalmia. The sympathizing eye, on the other hand, is likely to show the uncomplicated picture of this apparently specific form of uveitis. The observations of Milles,[14] Deutschmann,[15] Zimmermann,[16] Grunert,[17] Schirmer,[1b] Welt,[18] Asayama,[19] Blascheck,[20] Lenz,[21] Pöllot,[22] Meller,[23] and others showed the process in the sympathizing eye to be otherwise essentially the same as that seen in the exciting eye, which is usually the one available for histologic examination.

The most characteristic involvement is seen in the choroid. Round cell infiltration appears first in the middle and outer layers, leaving the choriocapillaris, at least for a time, free from change. The round cells, in the earlier stages, are found in irregularly placed groups but may become so numerous as to form a dense, confluent layer throughout the choroid, even causing a degree of thickening which is grossly evident on section. Among the round cells and sometimes in round cell-free areas there are found nests of epithelioid cells which, under low magnification, appear in the stained sections as pale patches contrasting sharply with the deeply staining masses of round cells. Particularly when they contain giant cells these collections of epithelioid cells closely resemble epithelioid tubercles. The round cells are usually composed predominantly of lymphocytes with an admixture of plasma cells, while neutrophilic polymorphonuclears and eosinophils may also be found. The choroidal involvement is seldom less severe than that in other parts of the uvea and often represents almost the entire extent of the process (Fuchs [2]).

In the iris the degree of involvement is extremely variable. The infiltration usually starts near the posterior surface, often behind the dilator and sphincter muscles which may become widely separated from the pigment epithelium by this infiltration. Epithelioid cells appear later

13. Ruge, S.: Arch. f. Ophth. **57**:401, 1904; **65**:135, 1907.
14. Milles, W. J.: Roy. Lond. Ophth. Hosp. Rep. **6**:48, 1886.
15. Deutschmann, R. H.: Beitr. z. Augenh. **1**:850, 1893.
16. Zimmermann, W.: Arch. f. Ophth. **42**:39, 1896.
17. Grunert, K.: Klin. Monatsbl. f. Augenh. **38**:1, 1900; **39**:833, 1901.
18. Welt: Rev. méd. de la Suisse Rom. **22**:408, 1902.
19. Asayama, J.: Arch. f. Ophth. **54**:444, 1902.
20. Blascheck, A.: Ztschr. f. Augenh. **9**:434, 1903.
21. Lenz, G.: Klin. Monatsbl. f. Augenh. **45**:468, 1907.
22. Pöllot, W.: Arch. f. Ophth. **81**:264, 1912.
23. Meller, J.: Arch. f. Ophth. **101**:122, 1920.

than the round cells and gradually replace them. The granulomatous process may involve the entire iris and extend backward into any exudate present in the posterior chamber. Giant cells are said to be less numerous here than in other portions of the uvea (Parsons [5]), although in one of my cases they were very numerous. "The granulomatous tissue, in contradistinction to tuberculosis, never grows out over the free surface of the iris" (Ginsberg [12]).

The ciliary body always shows infiltration, sometimes more marked than in the choroid. It begins in the loose layer of connective tissue and seldom involves, to any great extent, the ciliary muscle. Epithelioid masses may produce marked thickening of both ciliary and orbicular portions. Giant cells are often conspicuous in this region. I have repeatedly found a quite orderly row of them in the neighborhood of the elastic lamina.

In both the iris and the ciliary body the pigment epithelium becomes disorganized, and the cells proliferate and migrate.

The nonpigmented ciliary epithelium is more likely to remain intact, but eventually may become much disturbed. The cells proliferate and wander out along the planes of the zonula, and among them are found leukocytes and epithelioid cells. The epithelial cells may even contribute to the building of collections of epithelioid cells (Ginsberg [12]).

Samuels,[24] in a recent study of the conditions existing at the site of injury in cases of sympathetic ophthalmia, found the specific infiltration in the neighborhood of the wound in a high percentage of cases. In a series of eighty-eight cases in which suitable sections were available there were two cases in which the infiltration was limited to the site of the wound. Nine cases showed more involvement here than elsewhere. In two cases there was no specific involvement at the site of the wound, and in ten it was less marked here than elsewhere in the uvea. In the remaining fifty-eight cases there was "about the same amount of infiltration in the various divisions of the uvea," i. e., not particularly more marked or less marked at the site of the wound. Regarding the relative age of the process in the various parts of the uvea, the author found that generally the infiltration was older in the anterior segment as indicated by the more frequent occurrence here of giant cells and epithelioid cells, while posteriorly the infiltration consisted only of nodules of lymphocytes. Samuel's conclusions regarding the significance of these findings will be discussed elsewhere.

I have mentioned the remarkable predilection of the disease for uveal tissue and its tendency to spare the other ocular structures. This is indeed striking when one compares the lesion with one of a more

24. Samuels, B.: Tr. Am. Ophth. Soc. **30**:253, 1932.

invasive character such as frank tuberculosis or syphilis. On closer analysis, however, the apparently sharp delimitation of the process becomes less impressive. The granulomatous lesion commonly extends into the sclera along the sheaths of uveal tissue which accompany the perforating vessels and nerves (the so-called emissary channels) and from these foci there proceeds more or less marked infiltration of the scleral tissue proper. In this way the process may extend quite through the sclera but seldom invades, to any appreciable extent, the adjacent orbital tissue.

The optic nerve head commonly shows some infiltration. The retina is seldom involved to a marked degree. In one of Meller's [25] cases there were large tumor-like proliferations, but such cases are evidently rare. More commonly, there are only small, occasional, epithelioid foci growing through from the choroid. Fuchs [2a] noted involvement of the retina in one case of a series of thirty-five. Friedenwald [26] found epithelioid foci in the retina in ten of a series of twenty cases of sympathetic ophthalmia. In one case, in which there was a retinal detachment of long standing, I found similar foci among the folds of the retina. Dalén [27] described cellular nodules beneath the retina on an apparently intact lamina vitrea (Dalén foci) which, according to Fuchs,[2a] were composed exclusively of derivatives of the pigment epithelium. Ginsberg [12] commented, in effect, that while such proliferations of the pigment epithelium occur, perhaps they represent the first reaction in processes that precede the wandering through of the granulomatous lesion. It is apparently not uncommon to find such extensions of the choroidal lesions elevating the retina or growing into postretinal exudate.

The epithelioid cells everywhere show a marked tendency to phagocytose uveal pigment, a fact which is perhaps paralleled by Friedenwald's [26] recent observations regarding the cutaneous lesion at the site of intracutaneous injections of pigment, which will be discussed later.

Necrosis is rather rare in the lesion of sympathetic ophthalmia and, according to Meller,[28] differs from the caseation of tuberculosis in that it occurs in streaks or channels among and not in the center of the collections of epithelioid cells. Samuels [24] mentioned that "that liquefaction that is sometimes seen in streaks in large masses of specific infiltration is not to be confounded with the caseation of tuberculosis."

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25. Meller, J.: Arch. f. Ophth. **89**:437, 1914.

26. Friedenwald, J. S., in discussion on Woods and Little.[51d]

27. Dalén, A.: Mitt. a. d. Augenklin. d. Carolin. med.-chir. Inst. zu Stockholm **6**:1, 1904.

28. Meller, J.: Arch. f. Ophth. **89**:248, 1914.

OUTLINE OF CLINICAL FEATURES

The more purely clinical features of the disease will be dealt with only briefly. Recognition of the clinical picture of sympathetic ophthalmia in the exciting eye is rendered difficult because here, as a rule, there is also a more or less marked traumatic endophthalmitis in addition to the special form of inflammation. The clinician, then, directs his efforts rather toward recognition of those traumatized eyes which are liable to become the seat of sympathetic ophthalmia and, as such, should be enucleated. Such eyes are said to be sympathetically potent. Wounds in the so-called dangerous zone and those in which there are retained foreign bodies are particularly sympathetically potent. To avoid an occasional disastrous result through attempting too close a distinction between the sympathetically potent and the sympathetically nonpotent eye, the rule of the ophthalmologist in this regard is intentionally made broader than it perhaps need be. All eyes are regarded as sympathetically potent which have suffered perforating injuries which have not healed perfectly and especially those which have suffered from endophthalmitis or its results.

Enucleation may at times fail to prevent the development of sympathetic ophthalmia in the remaining eye even when that eye showed no evidence of inflammation at the time of enucleation. Microscopy with the slit lamp might perhaps explain some of these cases by demonstrating early changes not detectable by other methods of examination.

The following quotation from Butler [29] may serve to point out the importance of examinations with the slit lamp with regard to sympathetic ophthalmia:

> It is impossible to overestimate the importance of a slit-lamp examination, of repeated examinations, in cases in which there is the slightest suspicion of this formidable complication. Often the diagnosis depends absolutely upon the result of these investigations, and they must never be omitted. The verdict of the slit-lamp compels us to remove eyes which appear harmless and enables us to retain those that are apparently dangerous.
>
> The characteristic sign of a sympathetic inflammation, a sign which it shares with allied conditions such as tuberculous cyclitis, severe cyclitis in general, and with exudative choroiditis, is the presence of cells in the vitreous, the retro-lental space, and the anterior chamber; in a word, cells in the aqueous. Later signs are pellucid K.P. [Keratitis Punctata] and exudative nodules on the iris.
>
> If in the case of an injured eye, which is under suspicion of being a possible exciting eye, we examine the aqueous and fail to find cells in the anterior chamber, in the retro-lental space, or in the vitreous, then it is very improbable that the eye is dangerous from the sympathetic standpoint. At the present time there is not sufficient evidence to make the statement more positive.

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29. Butler, T. H.: An Illustrated Guide to the Slit-Lamp, New York, Oxford University Press, 1927.

If, on the other hand, in addition to the ordinary clinical signs we find an infiltration of the vitreous with cells, with or without cells in the retro-lental space, and the anterior chamber, then the presumption that the eye is dangerous is very greatly strengthened.

Finally, if cells are found in the same situations in the fellow eye, with or without more obvious signs such as K.P., and ciliary injection, then the eye is sympathising, and active treatment must be initiated at once, even if the signs of inflammation are slight.

Whenever the histologic picture of sympathetic ophthalmia is found in an enucleated eye, the danger of development of a sympathizing process may still exist for a number of weeks after enucleation.

In consideration of the clinical evidences of inflammation in a sympathizing eye, it is customary to differentiate between sympathetic irritation and sympathetic inflammation. While the former is sometimes the forerunner of the latter, it is not necessarily a part of sympathetic ophthalmia. It consists of such subjective symptoms as photophobia, lacrimation and, at times, pain or weakness of accommodation. Objective evidences of inflammation are lacking. Sympathetic inflammation, on the other hand, gives rise to the subjective and objective phenomena which are characteristic of sympathetic ophthalmia as occurring in the sympathizing eye. These phenomena may be summarized as those of a low grade progressive uveitis usually terminating in complete blindness and atrophy of the bulb, although more favorable outcomes are not uncommon.

The question of enucleation of an injured eye after a sympathizing process has broken out is discussed as follows by Salzmann [30] in Fuchs' "Diseases of the Eye," from which much of the foregoing clinical outline was abstracted:

It is conceivable that the sympathetic ophthalmia will course more mildly when the focus from which it has started is removed. On the other hand, the eye which excites the sympathy may retain some vision while the eye which suffers in sympathy may become entirely blinded. In such a case one robs the patient of the very last possibility of retaining vision by the enucleation of the injured eye. One should therefore not enucleate when the condition of the exciting eye is better than that of the sympathizing eye.

Enucleation rarely comes into consideration in connection with the sympathizing eye. Prophylaxis of course here falls by the way. Enucleation can only be justified by pain or disfigurement.

Aside from the prophylactic and possible palliative value of enucleation, the problems of therapy hardly fall within the scope of a paper of this kind. Mention might be made, however, of recent reports of

30. Salzmann, M., in Fuchs, Ernst: Diseases of the Eye, ed. 15, translated by E. V. L. Brown, Philadelphia, J. B. Lippincott Company, 1933.

Woods and Little, Gill and others of very favorable results of the therapeutic use of uveal pigment—a phase of the problem of etiology to which reference will be made later.

ETIOLOGY AND PATHOGENESIS

As early as 1844, Mackenzie [31] had considered three pathways by which sympathetic inflammation might be transmitted, namely, through the vessels by means of their anastomoses within the skull, along the ciliary nerves or through the retina and optic nerves. Concerning these possible routes, he said, "The vessels on the side of the injured eye, being in a state of congestion which may increase to inflammation, perhaps communicate a disposition to similar disease to the vessels on the opposite side, with which they anastomose inside the cranial cavity." And again, "The ciliary nerves of the injured eye might be the paths along which the irritation is conveyed, through the medium of the third and fifth pairs, to the brain, from which it is reflected along corresponding nerves of the opposite side." Concerning the optic nerves, he wrote, "It is extremely probable that the retina of the injured eye is in a state of inflammation which advances along the corresponding optic nerve to the chiasma. From there, the irritative condition to which the inflammation was due crosses over to the retina of the opposite eye, along its corresponding optic nerve." Mauthner,[32] in 1878, said of Mackenzie that his observations "contain very nearly all that has been discovered in this province in the last forty years." Reviewing the development of the theories of pathogenesis, Mauthner leads up to a statement of his own conclusions from which a few passages may serve to illustrate the mystery in which the problem was then clothed.

> We have, on the whole, no right at all to ask whether the sympathetic affection is transmitted along the optic nerves, or along the ciliary nerves. . . . For the transmission may be effected in both ways. But by this, however, we are not to understand that one and the same morbid process can be transmitted, now along the one path and now along the other. On the contrary, irritative and inflammatory conditions are transmitted from the optic nerve and retina, along the optic nerves; whilst those inflammatory processes which are chiefly observed in that portion of the eye which is nourished by the ciliary nerves, and especially in the uveal tract, are transmitted along the ciliary nerves.
>
> In the present state of our knowledge we know nothing of any . . . direct transmission [by way of blood vessels].

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31. Mackenzie, W.: Practical Treatise on the Diseases of the Eye, London, Longman [and others], 1830; ed. 2, 1835; ed. 3, 1839, and ed. 4, 1854. The quotations are from Mauthner.[32]

32. Mauthner, L.: Sympathetic Diseases of the Eye, translated by Warren Webster and James A. Spalding, New York, William Wood & Company, 1881.

It is, of course, hard to say wherein the irritative condition consists; but it is a fact that the irritation can propagate itself to the second eye. . . .

Some one may ask how it is possible for such a connection to exist between the eyes, by means of the optic nerves, in those cases in which the optic nerve of the eye first affected is in a stage of total atrophy. A cord of connective tissue cannot transmit such a sensorial irritation. Granted; but even if this is so, we cannot assume . . . that *all* the fibers of the optic nerve of the first eye are atrophic.

By the beginning of the twentieth century bacterial theories had been advanced in explanation of the etiology, and there had been recorded many fruitless attempts to attach significance to the finding of one or another of a variety of organisms in cases of sympathetic ophthalmia. These theories of etiology had become incorporated in new theories of pathogenesis which by this time constituted a formidable list.

Schirmer [1b] (1900) classified the then current theories as follows:

1. Pure nerve theories
   - (*a*) Optic nerve theory
   - (*b*) Ciliary nerve theory
2. Pure bacterial theories
   - (*a*) Transmission by metastasis
   - (*b*) Transmission by reversed venous flow
   - (*c*) Transmission by lymph channels
3. Combined theories
   - (*a*) Meyer's theory
   - (*b*) Schmidt-Rimpler's theory

Many of these theories need mention today only because of their historical interest. The pure nerve theories were based on the conception of transmission of irritation after the manner of transmission of sensory or motor impulses. Müller's [33] objection to the optic nerve theory, based on the fact that the nerve frequently is completely atrophic, and Mauthner's attempt to overcome this objection will serve to illustrate this point of view.

The theory of bacterial transmission by metastasis, while foreshadowed by Mackenzie's suggestion of a blood vascular route, was first advanced by Berlin [34] (1880). Parsons,[5] in reviewing these theories, singled out this one as being the most probable. He referred to the fact that certain tissues furnish sites of predilection for certain organisms such as tetanus bacilli or typhoid bacilli and suggested that the organism causing sympathetic ophthalmia "is pathogenic only for the eye." He drew an analogy between this disease and others which set up metastases, such as syphilis, tuberculosis and leprosy in which

33. Müller, H.: Arch. f. Ophth. **4**:363, 1858.
34. Berlin, R.: Samml. klin. Vortr. **186**:1529, 1880.

the lesions are subacute or chronic, and not purulent, and contended that the fact that sympathetic ophthalmia "manifests itself as a uveitis both in the exciting and in the sympathizing eye points to the same *causa causans.*" He concluded his discussion with the following hypothetic outline of events:

> The organism multiplies in the exciting eye; if this is removed early infection [of the other eye] does not occur, but if organisms have escaped in quantity into the circulation sympathetic ophthalmia may follow. The conditions of existence in the circulation and in other organs of the body are relatively bad, as is shown in the case of other organisms. It is probable that early encapsulation may occur in the exciting eye. As is well known bacteria may long lie dormant but viable in this condition. Slight injury or other cause may set them free, thus explaining the occurrence of sympathetic ophthalmia long after the first injury, though preceded at a short interval by inflammation in the exciting eye.

The theory of transmission by reversed venous flow was based on the idea that bacteria might reach the cavernous sinus and then be carried into the veins of the opposite eye by a reverse flow of blood induced by coughing or sneezing. The theory was advanced by Arnold,[35] in 1891, but received little support.

The theory of bacterial transmission by lymph channels meant, according to most of its proponents, transmission by way of the intervaginal (subdural and subarachnoid) spaces of the optic nerves and their communications within the cranial cavity. Leber [36] (1881) originated the theory, and Deutschmann,[37] in supporting it, suggested the name ophthalmia migratoria for the disease. The evidence adduced in support of this theory was largely the result of animal experimentation in which pyogenic organisms were injected into the vitreous. The most convincing result was the production of a papillitis in the opposite eye, but even this was obtained by only a few of the many workers in this field. Römer,[38] in this connection, said that no conclusions concerning the pathogenesis of sympathetic ophthalmia in man can be drawn from experiments on animals with pyogenic organisms.

Parsons,[5] Ginsberg [12] and others pointed out that clinical evidence does not support this theory since the disease in the sympathizing eye relatively seldom begins with a papillitis. S. R. Gifford,[39] on the other hand, mentioned the frequent occurrence of optic neuritis in the second eye, "sometimes as practically the only symptom."

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35. Arnold, J.: Virchows Arch. f. path. Anat. **124**:385, 1891.

36. Leber, T.: Arch. f. Ophth. **27**:272, 1881; **58**:325, 1904.

37. Deutschmann, R. H.: Ueber die Ophthalmia migratoria, Hamburg, Leopold Voss, 1889.

38. Römer, P.: Arch. f. Ophth. **55**:302, 1902.

39. Gifford, S. R.: Nebraska M. J. **14**:432, 1929.

E. Fuchs,[2a] in 1905, opposed the theory on histologic grounds.

More recently, A. Fuchs [40] (1925) examined portions of optic nerve in seventy-five cases of sympathetic ophthalmia, and in almost one third of the cases found what he regarded as definite evidence of involvement of the nerve in the specific process. This consisted of lymphocytic infiltration of the pia extending from the tip of the intervaginal space backward for from 1 to 2 mm., although small, isolated foci could be found as far as 12 mm. back along the nerve. Reviewing this work, Ginsberg [12] concluded that proof of the migration of the process over the optic nerve cannot be discovered in Fuchs' findings.

Meyer's [41] theory stated that the results of ciliary irritation in the injured eye depended on the presence or absence of bacteria in the opposite eye. If bacteria were present, sympathetic inflammation resulted; whereas, if bacteria were absent, the result was only a sympathetic irritation.

Schmidt-Rimpler's [42] theory was based on the assumption that irritation of the ciliary nerves of one eye exerts a reflex influence on the circulation and nutrition of the other eye, thus paving the way for infection by some unknown agent. H. Gifford [43] contended that this theory would not stand the "test of clinical experience." He asked "If sympathetic ophthalmia depends merely on the coincidence of ciliary irritation and the accidental presence of germs in the circulation, why should we never hear of sympathetic ophthalmia in the tedious ciliary irritation existing with the numerous cases of one-sided keratitis, whether of trachomatous, herpes, phlyctenular, or other origin?"

The bacterial theories are all open to the important objection that micro-organisms have rarely been found in eyes which are affected by sympathetic ophthalmia, and to those which have been found it has been impossible to attach any etiologic significance.[44] The toxic theory, based chiefly on these negative findings with regard to actual infection, attempted to explain the lesions of sympathetic ophthalmia as being due to the effects of bacterial metabolic products (Gorecki,[45] Rosenmeyer,[46]

40. Fuchs, A.: Ztschr. f. Augenh. **56**:275, 1925.

41. Meyer, E.: Rev. gén. d'opht. **9**:481, 1890 (quoted by Schirmer [1b]).

42. Schmidt-Rimpler: Arch. f. Ophth. (Abt. 1) **38**:199, 1892.

43. Gifford, H.: J. A. M. A. **34**:341, 1900; Ophth. Rec. **25**:344, 1916; also for review up to 1919, Wood, C. A.: Encyclopedia of Ophthalmology, Chicago, Cleveland Press, 1920, vol. 16, p. 12369.

44. The recent findings of J. Meller offer a striking exception to this statement.

45. Gorecki, in discussion on Trousseau: Compt. rend. Soc. d'opht. de Paris, April, 1891 (quoted by Schirmer [1b]).

46. Rosenmeyer, L.: Arch. f. Augenh. **28**:71, 1893.

Bacchi,[47] Praun,[48] and others). Parson's objection that the disease in the sympathizing eye continues (or may even commence) after removal of the exciting eye is based on the assumption that the exciting eye furnishes the only focus from which such toxic substances may emanate. The idea of an extra-ocular focus of infection is advanced in one of the more modern theories which will be discussed later.

Since 1900 many of the theories in Schirmer's list have been left by the wayside, while others have survived and appear, more or less modified, among the group of so-called modern theories of etiology and pathogenesis to which more detailed consideration will be given.

The cytotoxic theory of Galowin[49] (1904) assumed that degenerating cells in the exciting eye give rise to an autocytotoxin which is antigenically specific for uveal tissue. Galowin prepared a serum which, theoretically, contained this cytotoxin. Intra-ocular injection of the serum caused a severe iridocyclitis, while intravenous injection gave what Galowin believed were slight microscopic changes in the ciliary epithelium.

The mycotic theory advanced by Römer[38] (1902) and the so-called biologic theory proposed by H. Gifford[43] (1900) are variations of the older bacterial metastatic theory. The biologic theory assumes that germs surviving the struggle for existence in the first eye acquire an increased capacity for growing in uveal tissue. Transmission to the second eye occurs by way of the blood stream.

S. R. Gifford[39] pointed out the convenience of the biologic theory in explaining the improvement in the sympathizing eye which sometimes follows enucleation of the exciting eye. Removal of the first eye, he maintained, is comparable to elimination of a focus of infection. When improvement does not follow enucleation "it must be assumed that enough [germs] have already arrived so that the secondary focus is unable to destroy them." This, like the other theories of infection, has lacked the support of any conclusive evidence of infection in the lesions of sympathetic ophthalmia.

The more recent researches into the etiology and pathogenesis of sympathetic ophthalmia can be divided into three main groups which might be designated as follows: (1) investigations of the possible rôle of allergy either as the sole etiologic agency or as a factor in the production of the disease; (2) experiments based on the idea that the disease is caused by a filtrable virus; (3) efforts to explain the disease as a reaction to toxins (particularly tuberculous toxin) originating in some extra-ocular focus.

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47. Bacchi, A.: Internat. Ophth. Cong., Rome **6**:97, 1894.
48. Praun, E.: Die Verletzungen des Auges, Wiesbaden, J. F. Bergmann, 1899.
49. Galowin, S.: Klin. Monatsbl. f. Augenh. **7**:150, 1909.

The so-called anaphylactic theory of pathogenesis was founded on the work of Elschnig [50] who, in 1910 and 1911, in a series of articles, reported the results of his investigations of the antigenic properties of uveal emulsions.

Elschnig's experiments with rabbits and guinea-pigs tended to show that animals can be sensitized to homologous or heterologous uveal emulsions; that the uvea is antigenically organ specific and not species specific, and that the constituent of the uvea responsible for its antigenic properties is the uveal pigment. Elschnig employed complement-fixation methods to demonstrate the development of specific antibodies in animals immunized to uveal tissue emulsions.

Woods,[51] since 1917, has extensively investigated this problem. He confirmed Elschnig's findings concerning the antigenic properties of uveal pigment and obtained additional evidence by using perfusion methods in pigment-sensitized dogs. Both Elschnig and Woods produced an apparently anaphylactic uveitis in animals, which resembled sympathetic ophthalmia in man. Both by animal experimentation and by clinical investigation of human material, Woods has produced evidence to show that, following injury to the uveal tract, the appearance of pigment antibodies (as demonstrated by complement fixation) can be interpreted as indicating a developing immunity to uveal pigment. He consistently was unable to demonstrate such antibodies in cases of sympathetic ophthalmia. In his later work, Woods substituted the intracutaneous test (with uveal pigment as antigen) for the less practical complement-fixation test and found hypersensitivity to uveal pigment, as evidenced by a positive intracutaneous test, in cases of sympathetic ophthalmia.

Unfortunately, it is not possible here to recount in greater detail these interesting experiments and clinical investigations which have furnished a basis for the idea that sympathetic ophthalmia is an anaphylactic, or allergic, phenomenon caused by absorption of uveal pigment.

Other investigators have obtained experimental results agreeing, wholly or in part, with findings of Elschnig and of Woods.

Fuchs and Meller,[52] in 1914, were unable to demonstrate uveal antibodies in serums of patients with sympathetic ophthalmia.

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50. Elschnig, A.: Arch. f. Ophth. **75**:459, 1910; **76**:509, 1910; **78**:549, 1911. Elschnig, A., and Salus, R.: ibid. **79**:428, 1911.

51. (*a*) Woods, A. C.: Arch. Ophth. **46**:503, 1917; Tr. Sect. Ophth., A. M. A., 1917, p. 133; Arch. Ophth. **47**:161, 1918; J. A. M. A. **77**:1317, 1921; Arch. Ophth. **51**:451, 1922. (*b*) Woods, A. C., and Knapp, A.: ibid. **51**:560, 1922. (*c*) Woods, A. C.: Tr. Ophth. Soc. U. Kingdom **45**:208, 1925. (*d*) Woods, A. C., and Little, M. F.: Arch. Ophth. **9**:200, 1933.

52. Fuchs, A., and Meller, J.: Arch. f. Ophth. **88**:282, 1914.

Fodor,[53] in 1927, reported the results of a hundred examinations the results of which were somewhat in conflict with those of Woods. He agreed that antibodies are absent in sympathetic ophthalmia, but decided that it is unsafe to employ the results of cutaneous tests as a basis for enucleation.

Verhoeff [54] (1927) found the intracutaneous test negative in a case of sympathetic ophthalmia, contrary to Woods' experience.

Berens and others [55] in 1927 reported negative results of intracutaneous tests in eighteen cases "which," they wrote, "should be expected if Woods' findings are correct, as no case presented signs or symptoms of inflammation."

S. R. Gifford,[39] in 1929, stated "we have made tests on two cases of sympathetic ophthalmia and two of favorably reacting penetrating wounds, without obtaining any positive skin tests."

Gill [56] (1930) reported positive intracutaneous tests in sympathetic ophthalmia and negative tests in other diseases. He also noted that "clinical improvement, at times spectacular, follows the employment of uveal pigment therapy in sympathetic ophthalmia, provided it is used early in the disease. Enucleation is often avoided by using pigment therapy early in sympathetic ophthalmia."

A great many objections have been raised to the idea that sympathetic ophthalmia is caused by allergy toward uveal pigment. The antigenic properties of the uvea (considered as an organ) are not admitted as proved beyond doubt, and the concept that in sympathetic ophthalmia one becomes allergic to his own uveal pigment is considered untenable by many. One of the chief objections is expressed by S. R. Gifford [39] as follows: "On such a theory, sympathetic ophthalmia would be expected to occur fairly often following any iridocyclitis, whereas it occurs almost exclusively following a penetrating wound."

Another of the more interesting of the modern theories of etiology is the tuberculotoxic theory advanced by Guillery [57] in 1923. The marked similarity of the lesions of sympathetic ophthalmia to certain tuberculous lesions suggested to Guillery the possibility that tuberculous toxin might be the cause of this peculiar disease entity. This idea was also given support by the results of his experiments with various other bacterial toxins and other poisons in which exudative and pro-

53. Fodor, G. I.: Klin. Monatsbl. f. Augenh. **79**:759, 1927.

54. Verhoeff, F. H.: Arch. Ophth. **56**:28, 1927.

55. Berens, C., and others: Atlantic M. J. **30**:547, 1927.

56. Gill, W. D.: South. M. J. **23**:885, 1930.

57. Guillery, H.: Ztschr. f. Tuberc. **38**:1, 1923; Arch. f. Augenh. **94**:143, 1924; München. med. Wchnschr. **72**:298, 1925; Klin. Monatsbl. f. Augenh. **76**:567, 1926; Arch. f. Augenh. **99**:63, 1928.

liferative ocular lesions had been produced in rabbits. In his earlier experiments Guillery showed that a reaction might be obtained in tissues remote from the source of the tuberculous toxins. He introduced semipermeable capsules containing live tubercle bacilli into the peritoneal cavities of rabbits. Necrosis of the liver with proliferation of bile ducts and reticulum developed, while in the vicinity of the capsule there was the usual foreign body (tuberculoid) reaction. By this method, however, Guillery was unable to produce disease of the eyes even when they were injured by various means.

Guillery then inserted his little capsules directly into the eyes of rabbits using the ciliary pouch method and, later, direct introduction into the vitreous chamber. There developed, first in the inoculated eye and somewhat later in its fellow, lesions which Guillery believed to be identical with those of sympathetic ophthalmia. He therefore concluded that tuberculous toxin is the cause of the disease.

To duplicate more closely the conditions which he conceived to exist in the case of human sympathetic ophthalmia, Guillery attempted to supply tuberculous toxins from an extra-ocular focus in the presence of a traumatic lesion of one eye of a rabbit. A capsule containing tubercle bacilli was introduced into the orbit through a cannula, and a wound of the ciliary body of one eye was made with a lancet. The result was a uveitis of the injured eye followed by similar changes in the uninjured eye.

The experimental results of Guillery have been essentially confirmed by Kolen [58] (1928) and by Poos and Sartorius [59] (1930), but these workers and others have questioned Guillery's conclusions. Von Szily [60b] (1926) reported that a test of the Guillery method on twenty animals showed negative results in respect to the undisturbed eyes, while the inoculated eyes showed a wide range of reactions including (in five cases) typical nodular tuberculosis. Some of von Szily's capsules, tested in glycerin bouillon, showed permeability to tubercle bacilli. Marchesani [61] (1928) doubted that the capsules used by Guillery could be made entirely impermeable to tubercle bacilli. Guillery, on the other hand, discussed at length the question of sterility of his capsules and their impermeability to bacteria. The failure of tubercles to develop in the immediate vicinity of a capsule introduced into the vitreous was taken as evidence of its imperviousness to bacteria, since tubercles formed at the site of inoculation when the inoculum was not enclosed in a capsule.

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58. Kolen, A.: Russk. j. oftal. **8**:320, 1928.

59. Poos, F., and Sartorius, F.: Arch. f. Ophth. **124**:565, 1930.

60. von Szily, A.: (*a*) Klin. Monatsbl. f. Augenh. **72**:593, 1924; (*b*) Deutsche med. Wchnschr. **38**:1598, 1926.

61. Marchesani, O.: Klin. Monatsbl. f. Augenh. **81**:868, 1928.

A proper evaluation of Guillery's contribution must await further experimental investigation.

Because of repeated failure of investigators to demonstrate bacteria in the lesions of sympathetic ophthalmia, attempts have been made to explain the disease on the basis of a filtrable virus. Von Szily,[60a] in 1924, using material from human corneal herpes, produced uveitis in rabbits, which, in some cases, was transmitted to the opposite eye. His procedure, briefly, was as follows: He first inoculated a rabbit's cornea by scarification and after from two to three days, when a characteristic keratitis had developed, took off the superficial layers of the cornea and used this material for subsequent inoculations. A small fragment of the material was then introduced into one eye of each of a number of rabbits. The site of inoculation was a so-called ciliary pouch made by separating the ciliary body from the sclera through a small corneal incision.

Uveitis of the inoculated eye regularly resulted. After about two weeks, when this reaction was beginning to subside, about 10 per cent of the animals showed iridocyclitis of the opposite eye—usually of a more severe form than that which had been observed in the inoculated eye.

Histologic sections of both eyes, in these cases, showed a picture resembling that of sympathetic ophthalmia. Sections of the papilla and optic nerve showed a similar infiltration, and there were also foci of infiltration in the chiasm and farther back along the optic tract. In addition, meningitis developed and, in 50 per cent of the cases, corneal herpes of the intact eye. Von Szily concluded, cautiously, that he had been able "through an invisible exciting cause to produce disease processes coinciding with human sympathetic ophthalmia in the essential points (injury of the ciliary region, transmission to the second eye of similar disease)."

Abe,[62] in 1926, and Velhagen,[63] in 1928, confirmed the findings of von Szily, while Marchesani,[64] repeating the experiments, obtained negative results.

In this country, in 1927, Gifford and Lucic [65] duplicated von Szily's results and further demonstrated the presence of virus in the second eye by inoculations from this eye to a ciliary pouch in another animal. The second animal, in turn, showed involvement of the second eye, and a further successful transfer to the cornea of a third rabbit showed transmission of the virus through three generations from the sympa-

62. Abe, T.: Arch. f. Ophth. **117**:375, 1926.
63. Velhagen, K., Jr.: Arch. f. Ophth. **119**:325, 1928.
64. Marchesani, O.: Arch. f. Augenh. **97**:575, 1926.
65. Gifford, S. R., and Lucic, L. H.: J. A. M. A. **88**:465, 1927.

thizing eye. Gifford and Lucic's sections, like those of von Szily, indicated extension of the process by way of the nerves and chiasm to the other eye. This they confirmed by positive inoculations with material taken from various points along this route. They also showed that uveitis of both eyes could be produced by injection of the virus into the region of the chiasm. The authors concluded that "the possibility of a filtrable virus with neurotropic properties similar to those of the herpes virus being the cause of sympathetic ophthalmia is given some support by this work."

These experiments represent the closest approach that has been made to the experimental production of sympathetic ophthalmia, but there are serious objections to the virus theory which are yet to be overcome. While the migration of the virus infection is clearly shown to proceed by the optic nerve route in the case of herpetic virus lesions in rabbits, no such migration has been conclusively demonstrated in the case of human sympathetic ophthalmia. The associated meningitis likewise is not characteristic of the human disease. Neither von Szily nor Gifford and Lucic claimed that herpes virus is the cause of sympathetic ophthalmia, but their findings suggest, in the words of the latter workers, "the possibility that a virus, perhaps not dissimilar to the herpes virus, may be the cause."

Attempts to demonstrate the presence of a virus by inoculation of animals with material from human cases of sympathetic ophthalmia have, to say the least, furnished no support for the virus theory. Marchesani,[66] Undelt,[67] Gifford and Lucic,[68] Meesmann and Volmer,[69] and Lešer [70] all attempted such inoculation but with essentially negative results. The method usually employed was to introduce portions of diseased human eyes into ciliary pouches in a number of rabbits. Only rarely was any disturbance produced in the second eye of a rabbit so treated, and the value of even these meager results seemed slight on the basis of histologic examination.

Samuels [24] (1932), from a study of the anatomic findings in a large series of cases of sympathetic ophthalmia, presented evidence which, in his opinion, lends support to the theory that the disease is caused by a primary infection. He attached particular significance to the finding of two cases in which the typical infiltration was limited to the site of injury, furnishing examples of apparently primary lesions at the site of a wound and supporting the idea that in sympathetic ophthalmia a specific infectious agent enters at this point.

66. Marchesani, O.: Klin. Monatsbl. f. Augenh. **75**:218, 1925.
67. Undelt, J.: Klin. Monatsbl. f. Augenh. **76**:825, 1926.
68. Gifford, S. R., and Lucic, L. H.: Arch. Ophth. **1**:468, 1929.
69. Meesmann, A., and Volmer, W.: Arch. f. Augenh. **98**:271, 1927.
70. Lešer, O.: Časop. lék. česk. **67**:934, 1928.

This opinion is in accord with the earlier conclusion of Marchesani [71] who, on similar grounds, considered that the lesion in the exciting eye was due to a noxa entering at the site of injury.

Woods and Little,[51d] in a recent report, discussed the development of "a new school of thought as to the pathology of sympathetic ophthalmia." Observations of Key,[72] Marchesani,[73] Riehm,[74] and others have given more and more substantial form to the idea, suggested by Woods in 1925, that sensitization of the uveal tissue (of both eyes) renders it susceptible to the action of other noxious agents. Woods and Little offered further evidence in support of this explanation of sympathetic ophthalmia by recording and analyzing the results of intracutaneous pigment tests in one hundred and fifty-three patients.

In this series positive pigment reactions occurred only in cases of penetrating wounds, either operative or traumatic. Among twenty patients with sympathetic ophthalmia, there were eighteen who gave positive reactions to pigment tests.

Five patients were grouped as having delayed, noninfectious, postoperative uveitis, apparently a new clinical entity. All of these patients showed hypersensitivity to uveal pigment as shown by intracutaneous tests, but in none of this group did sympathetic ophthalmia develop. Two patients of this group were given courses of pigment therapy which were attended by remarkable clinical improvement and loss of sensitization as shown by negative intracutaneous tests. Among the group of patients with sympathetic ophthalmia those treated with uveal pigment, according to the authors, did vastly better than those not treated with pigment.

In the light of these and other observations, the authors conclude that "in sympathetic ophthalmia hypersensitivity to uveal pigment is a general rule, although patients with acute exacerbations of the disease may have a definite phase in which the intracutaneous test is negative." The occurrence of cases of chronic uveitis in which hypersensitivity to pigment developed without sympathetic ophthalmia supported the contention that "pigment hypersensitivity does not appear to be the cause per se" but that "some other factor enters into the disease."

An interesting feature of Woods and Little's report is an account of the histologic study of specimens of skin taken from the site of intracutaneous pigment tests. The study was made at the suggestion and with the collaboration of Jonas S. Friedenwald. Skin from two normal persons, who had been given intradermal injections of pigment

71. Marchesani, O.: Ztschr. f. Augenh. **56**:275, 1925.

72. Key, B. W.: Am. J. Ophth. **9**:574, 1926.

73. Marchesani, O.: Zentralbl. f. d. ges. Ophth. **22**:804, 1930.

74. Riehm, W.: Deutsche med. Wchnschr. **55**:907, 1929; Arch. f. Ophth. **123**: 361, 1930; Arch. f. Augenh. **105**:82, 1931.

two weeks before, showed "a moderate infiltration with monocytes and lymphocytes around the injected pigment. The larger part of the pigment remained free in the tissues not ingested by phagocytic cells." Sections of skin from two persons giving positive intracutaneous tests showed the deposits of pigment "infiltrated with great numbers of epithelioid cells and giant cells in which the granules were phagocytosed." Both of the latter specimens were from persons cured of sympathetic ophthalmia, the excisions being made two and four weeks, respectively, after the injection of pigment.

Friedenwald,[26] in discussion of these results, emphasized the resemblance of the positive cutaneous lesions to the uveal lesion in sympathetic ophthalmia.

Within the past year, Meller [75] reported bacteriologic observations which are of interest. In the laboratory of E. Löwenstein, by a special culture method, it is reported, virulent tubercle bacilli have been recovered first, from the blood stream in a case of sympathetic ophthalmia, then from the ocular tissue in a case of spontaneous iridocyclitis and, lastly, from the circulating blood and the tissues of the exciting eye in a typical case of sympathetic ophthalmia.

The last-mentioned case was one of a perforating injury in which a sympathizing inflammation was noted six weeks after the injury. On the day of the outbreak of disease in the second eye a blood culture was made, the injured eye was enucleated, and tissue from its interior was cultured.

The histologic changes in the enucleated eye were reported in detail by Meller, who epitomized them as showing "das volle Bild der sympathisierenden Uveitis in allen seinen Einzelheiten" (the complete picture of sympathetic uveitis in all its details).

The cultures of ocular tissue showed a luxuriant growth of tubercle bacilli, while the cultures of the blood, although also positive, showed only a sparse growth. Blood taken ten days after enucleation showed the bacteremia still present. The virulence of the organisms was proved by inoculation into animals.

Meller expressed the belief that sympathetic ophthalmia is a bacterial disease caused by the tubercle bacillus. He pointed out that particularly people who have a bacteremia at the time of injury to the eye are in danger of developing a tuberculous uveitis. When the tuberculosis is of a proliferative character it can be called sympathetic ophthalmia, and the other eye is likely to become involved in the process. According to Meller, uveitis does not develop in all of those cases of injury in which there is a coexisting bacteremia, and, on the other hand, bacteremia

75. Meller, J.: Wien. klin. Wchnschr. **45**:33, 1932; Ztschr. f. Augenh. **77**:1, **79**:75, 1932.

occasionally causes a uveitis in an untraumatized eye, but only when the bacteria are detained in the walls of the vessels. Hemorrhage into the tissues produces particularly favorable conditions for invasion and incubation of the bacteria brought by the circulating blood. The importance of wounds of the ciliary body is explained on this basis. The author admits the possibility of exogenous tuberculous infection at the site of injury but believes that the infection is usually hematogenous.

Meller emphasizes the vascular phenomena in various portions of the eye as being of particular importance, since the proliferation of cells into the vessels favors spread of the infection by way of the blood stream. The involvement of the second eye is regarded as a metastatic phenomenon caused by blood-borne virulent tubercle bacilli from the first eye. Many of the peculiarities of the disease can be explained, according to Meller, by this concept.

Interesting and suggestive as are the findings of Meller, they can hardly justify the conclusion that the enigma of sympathetic ophthalmia has at last been solved. Meller's work must first be confirmed. It must further be shown that the bacilli can regularly be recovered from the ocular tissues in these cases, and the cultural method, or methods, employed must be of proved reliability.

CONCLUSIONS

Any attempt to summarize and draw conclusions concerning the various disputed aspects of sympathetic ophthalmia would serve only to add opinions of doubtful value to an already long and conflicting list. The reader, I believe, might better be left to form his own conclusions or to await further elucidation of the many interesting problems which the disease presents.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—Knighthood has been conferred on Robert Muir, professor of pathology in the University of Glasgow.

Roy Lee Moodie, anatomist and paleopathologist, has died at the age of 54. He made important contributions to the study of the structural evidences of ancient disease.

Michael Heidelberger, associate professor of biological chemistry at Columbia University, has been awarded a Guggenheim fellowship for research at the University of Uppsala, Sweden, on the molecular weight of thyroglobulin.

Richard Kockel, professor of forensic medicine in the University of Leipzig, has died at the age of 69.

Ernest Scott, professor of pathology in the Ohio State University since 1915, has died of coronary thrombosis, at the age of 58.

Society News.—At the meeting of the American Association of Pathologists and Bacteriologists in Toronto, March 29 and 30 last, William Boyd was elected president, N. C. Foote vice president, H. T. Karsner secretary and F. B. Mallory treasurer. The next meeting will be held at the Cornell University Medical College, New York, on April 18 and 19, 1935.

The annual meeting of the American Society for the Study of Neoplastic Diseases (president, Max Cutler) will take place in Washington, D. C., on September 6 to 8, 1934.

The William Wood Gerhard Gold Medal of the Pathological Society of Philadelphia was presented to George H. Whipple of the University of Rochester School of Medicine and Dentistry at a meeting on April 12, 1934. At that time Dr. Whipple gave the Annual Conversational Lecture of the society on "Regeneration of Hemoglobin and Blood Plasma Proteins Controlled by Diet Factors."

Medicolegal News.—The University of Michigan has organized an Institute for Law Enforcement Officers. Recently four all-day sessions, attended by more than a hundred officials, were held at Ann Arbor with lectures and discussion on poisoning, the examination of dead bodies, wounds, personal identification and other topics of criminologic interest.

Gibbs Prize to Be Awarded.—The New York Academy of Medicine announces that a sum of about $800 is available under the Edward M. Gibbs Memorial Prize toward original research in diseases of the kidney in 1934. Candidates for the award must be physicians who have been graduated at least three years and who are residents of the United States. They must submit evidence of research already performed and facilities to prosecute research on the causation, pathology and new methods of treatment of diseases of the kidney. The award may be continued through not more than three years to any one person. Applications with the required evidence should be sent to the New York Academy of Medicine, 2 East One Hundred and Third Street, New York, before June 1, 1934.

Historic Microscopic Sections.—The nephritis clinic at Guy's Hospital, London, has presented to the department of physiology of the University of Cincinnati microscopic sections of three kidneys decribed by Richard Bright in his "Reports of Medical Cases," 1827, and in *Guy's Hospital Reports*, 1838.

Abstracts from Current Literature

Pathologic Anatomy

RUPTURE OF THE AORTA. F. C. NARR and A. H. WELLS, Am. Heart J. **8**:834, 1933.

An interesting case is described of partial rupture of the aorta a little above the attachment of the aortic valve, due to so-called idiopathic medial necrosis, followed by dissecting aneurysm, with subsequent rupture of the outer coat into the pericardium. This rupture was rapidly fatal. The patient was a physician, 29 years old.

R. J. NIEHAUS.

THE INCIDENCE AND SEVERITY OF ARTERIOSCLEROSIS IN THE ORGANS FROM 500 AUTOPSIES. WILLIAM B. WARTMAN, Am. J. M. Sc. **186**:27, 1933.

An analysis of the incidence and severity of arteriosclerosis in the organs in 500 unselected autopsies is presented. The order of frequency with which the arterioles and small arteries of the organs were affected was: spleen, brain, kidney, suprarenal gland, pancreas, heart, gastro-intestinal tract, lungs, liver and diaphragm. This is in agreement with the observations of most investigators. The arteries of the organs which were most frequently involved were also most markedly affected; conversely, those of organs least often involved showed mild degrees of arteriosclerosis. The vessels of the diaphragm were frequently implicated. The incidence and degree of arteriosclerosis increased with the age. The reports from the literature and the results of this study indicate that a generalized arteriosclerotic process of a degree sufficiently advanced to be of clinical importance occurs infrequently.

AUTHOR'S SUMMARY.

RENAL LESIONS ASSOCIATED WITH MULTIPLE MYELOMA. E. T. BELL, Am. J. Path. **9**:393, 1933.

Renal insufficiency develops frequently in multiple myeloma, especially in the advanced stages. In some instances it is due to arteriosclerosis; in others it is caused by pyelonephritis resulting from compression of the spinal cord or hypertrophy of the prostate. The only direct effect of multiple myeloma on the kidneys is that due to the formation of tubular casts of Bence-Jones protein that obstruct the tubules and cause atrophy. When large numbers of tubules are obstructed, extensive atrophy of the cortex and renal insufficiency ensue. There is no evidence that the Bence-Jones protein injures either the tubules or the glomeruli. Cortical atrophy is caused by obstruction and should not be interpreted as "nephrotic contracted kidney." In one instance renal insufficiency was apparently caused by the accumulation of a highly concentrated protein solution in the glomerular capillaries. In two other instances the same condition was found in a few capillaries.

AUTHOR'S SUMMARY.

EXTREME ALTERATION OF THE AORTIC VALVE IN SYPHILITIC AORTITIS. O. SAPHIR and J. STASNEY, Am. J. Path. **9**:431, 1933.

Two cases of syphilitic aortitis with involvement of the aortic valve are reported. In both instances the involvement of the valve reached extreme degrees, causing transformation of one sinus of Valsalva into a cavity in one instance and almost complete disappearance of a part of one sinus of Valsalva in the other. Reports of only eight similar cases were found in the literature. Histologically, granulation tissue and much fibrosis and hyalinization were found within the commissures and

the adjacent parts of the adherent aortic cusps. The granulation tissue had spread from the aortic intima through the commissures and also through the base of the cusps into the cusps themselves. The widening of the commissures, which is pathognomonic of syphilitic involvement of the aortic valve, was the result of adhesions between the cusps of the aorta and the corresponding aortic wall. The widening of the commissures, therefore, cannot be explained on a mechanical, but must be explained on an inflammatory, basis.

AUTHORS' SUMMARY.

RHEUMATIC HEART DISEASE WITHOUT VALVULITIS. C. Z. GARBER, Am. J. Path. **9**:443, 1933.

Seventeen cases have been noted in the literature in which the diagnosis of rheumatic fever was made at autopsy and in which all the valves of the heart were apparently free from rheumatic lesions; all these cases exhibited myocarditis with Aschoff bodies present, and in four cases pericarditis was also present. An additional case of chronic rheumatic fever is reported, based on present criteria, in which the valves of the heart were free from rheumatic lesions. Aschoff bodies were not found, and the diagnosis of rheumatic fever depended on the presence of characteristic lesions in the left auricle, scars in the media and diffuse infiltrations of the heart and of the adventitia of the aorta and the pulmonary artery by inflammatory cells. Death occurred one year and eight months after the first symptoms of congestive heart failure, following administration of quinidine. An embolus, accounting for the mode of death, was found in the right internal carotid artery. It is believed that this was formed on the rheumatic endocardial lesion in the left auricle.

AUTHOR'S SUMMARY.

THE RELATION OF HEPATITIS TO CHOLECYSTITIS. J. F. NOBLE, Am. J. Path. **9**:473, 1933.

Infiltration of the portal spaces by lymphocytes and polymorphonuclear leukocytes is seen almost constantly in the liver at autopsy. This portal infiltration seems to have no particular relation to generalized infections or to any specific type of disease and apparently bears no relation to the nonclinical cholecystitis frequently found in routine postmortem examinations. The latter is seen less frequently in the female than is clinical cholecystitis and is more frequent in the younger age groups. In the series of autopsies studied cirrhosis occurred too rarely to justify the conclusion that the hepatitis described has an etiologic relation to cirrhosis.

AUTHOR'S SUMMARY.

BONE MARROW IN TULARAEMIA. R. D. LILLIE and E. FRANCIS, Pub. Health Rep. **48**:1127, 1933.

Focal lesions were almost constantly present in the bone marrow of rodents with acute tularemia in the five species of rodents in which the marrow was systematically studied. They were frequent in the bone marrow also of rabbits and guinea-pigs with subacute tularemia. The focal lesions in the marrow in subacute tularemia often became granulomatous, but also often remained as simple focal necrotic changes, while lesions in other organs were granulomatous. There was a greater tendency to granulomatous reaction in rabbits which had been repeatedly inoculated with living cultures of Bacterium tularense; but in some of these in which marked granulomatous reactions were present in the lungs within a few days after the last inoculation, the lesions were in all probability assignable to the inoculation carried out a month or more previously. Aside from focal lesions, there appeared to be some destructive action affecting the more mature cell forms of the marrow. It appears probable that focal lesions may be encountered in the bone marrow of man when a more extensive search is made.

A Case of Gonococcal Endocarditis with Rupture of the Aortic Valve and Death. William B. Porter, Heart **16**:201, 1933.

A case of gonococcic endocarditis is reported in which rupture of the aortic cusp was heard to take place during life. The rupture was followed immediately by acute and fatal edema of the lungs. A Negress, aged 16, entered the hospital with acute gonococcic vaginitis of four weeks' duration and acute arthritis of two days' duration. The heart showed no demonstrable enlargement. A soft systolic murmur was heard over the precordium. The pulse rate was 118 and regular. The blood pressure was 120 systolic and 65 diastolic. Three days after admission acute gonococcic conjunctivitis developed in the left eye. Nine days after admission the systolic murmur had definitely increased over the base of the heart, and a low-pitched diastolic murmur was audible along the left border of the sternum. A blood culture showed a growth of gonococci. Seventeen days after admission, while the heart was being auscultated, the diastolic murmur suddenly increased in intensity and became musical. The patient soon became dyspneic. Moist râles were heard over both lungs, and pink, frothy fluid began to flow from the nose and mouth. The pulmonary edema progressed rapidly. The pulse rate rose to 140. The patient became unconscious and died about twenty minutes after the onset of the pulmonary symptoms. Autopsy, performed the following day, revealed edema and congestion of the lungs. The right lung weighed 590 Gm., and the left, 600 Gm. There was a thin, blood-tinged fluid in the bronchi and the myocardium was soft and pale. The heart weighed 310 Gm. There was perforation of the two anterior aortic cusps, one perforation being 6 mm. and the other 4 mm. in diameter. A low verrucous, friable, pinkish-white vegetation was seen on the margins of the perforations. Microscopically, there were: edema, fibrinous exudation, leukocytic infiltration and moderate histiocytic proliferation in the cusps of the aortic valve, a small abscess in one cusp, scattered foci of interstitial polymorphonuclear infiltration in the myocardium, pulmonary alveoli filled with serous fluid in which were alveolar phagocytes containing blood pigment, and pulmonary congestion. Porter concludes that the change in the diastolic murmur was due to rupture of the aortic cusps, resulting in aortic regurgitation, cardiac failure and pulmonary edema.

Esther Marting.

Renal Lesions in Eclampsia and Nephritis of Pregnancy. D. Baird and J. S. Dunn, J. Path. & Bact. **37**:291, 1933.

The common lesion in the kidneys in fatal eclampsia is glomerular and is characterized by thickening of capillary walls and of endothelium, leading to some degree of obstruction to the flow of blood. Tubular changes are less constant, and may be of secondary import. A degree of this lesion probably constitutes the anatomic basis of the albuminuria of pregnancy. In a case of renal cortical necrosis diffuse glomerulitis had existed prior to the occurrence of the necrosis.

Authors' Summary.

Interpretation of Renal Changes in Lipoid Nephrosis. P. Gérard and R. Cordier, Arch. internat. de méd. expér. **8**:225, 1933.

Gérard and Cordier injected normal serum and serum rich in cholesterol intraperitoneally in a series of salamanders and frogs under varying conditions. Then the kidneys were fixed in solution of formaldehyde, and frozen sections were made and examined with Nicol prisms under polarized light. They found that cholesterol cannot filter through normal glomerular epithelium. However, if this is rendered permeable by previous injection of egg albumin, cholesterol comes through and is deposited in the epithelium of the convoluted tubules. In clinical lipoid nephrosis the albuminuria renders the glomerular epithelium permeable to cholesterol, which thus enters the convoluted tubules and is there reabsorbed by the epithelium.

Jacob Klein.

CALCIFICATION OF THE CARDIAC SKELETON. WILLY GIESE, Beitr. z. path. Anat. u. z. allg. Path. **89**:16, 1932.

According to Tandler, the skeleton of the heart consists of the fibrous framework which connects the musculature of the ventricles and the atria. In more than 700 autopsies, calcification of this portion of the heart was observed 72 times. There were 30 cases of calcification of the annuli fibrosi, 2 of calcification of the aortic valves and 22 of combinations of both. In 8 cases the calcification followed inflammation. Calcification did not occur as a rule before the fiftieth year of life and was more extensive after the sixth decade. The calcification was preceded by fatty degeneration, atheroma, focal necrosis and hyalinization of the collagenic fibers. The calcification often caused mitral or aortic vitia, and in a few cases calcification of the pars membranacea septi produced heart block. Senility, mechanical injuries and disturbance of the calcium metabolism may be the etiologic factors in this condition.

C. ALEXANDER HELLWIG.

LIPOID SUBSTANCES IN CELLS OF MESENCHYMAL ORIGIN. J. GOLDMANN, Virchows Arch. f. path. Anat. **287**:587, 1933.

Goldmann believes that two forms of lipoid are to be found in the normal mesenchymal cell. One form, called by him "integral" lipoid, is an integral part of the cell and is always present. The other form is the "infiltrative" lipoid, the presence of which is dependent on the intake of lipoids.

A number of rabbits, guinea-pigs, rats and mice were fed a 5 per cent solution of cholesterol in oil for a period of from five to fifteen days. The animals were then killed, and various organs and blood smears were examined. Goldmann used his own modification for staining lipoid with sudan and naphthol-hematoxylin. With this method it was possible to demonstrate the normal "integral" lipoid within the leukocytes of the blood, as well as in cells of the various tissues. The intracellular lipoid structure seems to be largely dependent on the protein structure; in pathologic conditions the lipoid granules become separated from the protein and may disappear entirely. The reticulo-endothelial cells were found to be filled with "infiltrative" lipoid throughout, without apparent damage of the cellular structure.

W. SAPHIR.

THE PANCREATIC ISLETS OF THE NEW-BORN INFANT OF A DIABETIC MOTHER. K. A. HEIBERG, Virchows Arch. f. path. Anat. **287**:629, 1933.

A woman with severe diabetes mellitus passed through pregnancy and delivery without any untoward events. The diabetic condition improved after delivery. The infant died two days after birth with symptoms of hypoglycemia; the blood sugar was 60 mg. per hundred cubic centimeters. Microscopic examination of the pancreas revealed marked hypertrophy and hyperplasia of the islets.

W. SAPHIR.

KÖHLER'S DISEASE OF THE TARSAL NAVICULAR BONE IN IDENTICAL TWINS. P. ESAU, Virchows Arch. f. path. Anat. **287**:634, 1933.

Köhler's disease, or os naviculare pedis retardatum, consists in a malformation of unknown cause. Although the disease may occur at times without any clinical symptoms, it is usually recognized fluoroscopically by the multitude of osseous nuclei and by the disturbances in calcification of the navicular bone. Esau presents the history and roentgenograms of a typical case of this disease in two single ovum twins. He concludes that Köhler's disease is due to a disturbance of embryonic development at an early stage of that development.

W. SAPHIR.

REGRESSION OF THE SACRAL INTERVERTEBRAL DISKS AND ITS POSSIBLE RELATION TO SACRAL CHORDOMA. R. SCHWALBE, Virchows Arch. f. path. Anat. **287**:651, 1933.

In this comprehensive and well illustrated article Schwalbe undertakes to follow the fate of the human sacral intervertebral disks. It is known that these disks are fully developed in the early stage of life, and that they undergo complete regression before osseous union of the five sacral vertebrae takes place.

Careful and thorough histologic examination was made of sixty-six sacral bones of persons of various ages. The youngest person whose sacral bones were examined was a premature infant 33 cm. long, while the oldest was a woman aged 84.

The phases of regression are histologically recorded and described. Osseous union of the sacral vertebrae takes place at the end of the second decade. But even in the later stages of life evidence of continued osseous and cartilaginous activity was frequently observed.

Rudimentary intervertebral segments of the chorda were found up to the fifth decade. The possible development of chordoma from cells of these rudimentary rests is discussed.

W. SAPHIR.

THE POROTIC FORM OF PAGET'S DISEASE OF THE SKULL. B. PINES, Virchows Arch. f. path. Anat. **287**:714, 1933.

A thorough study of a typical case of Paget's disease reveals that a porotic form exists, that is confined chiefly to the skull. Multilocular areas of porosis and markedly increased periosteal appositional growth of bone characterize this rare form of Paget's osteitis deformans.

W. SAPHIR.

CYST OF THE ROOF OF THE THIRD CEREBRAL VENTRICLE. M. A. BASS, Virchows Arch. f. path. Anat. **287**:790, 1933.

Cysts of the third cerebral ventricle originate either from the ependyma or from the choroid plexus. Only four ependymal cysts and two cysts of the choroid plexus were found described in the literature. Bass adds a further case of cyst of the choroid plexus. A woman, aged 22, died with symptoms of cerebral tumor. Autopsy revealed a cherry-sized cyst on the roof of the third ventricle, which had led to obstruction of the circulation of fluid, with subsequent hydrocephalus. The cyst was lined with cylindric plexus epithelium and contained a network of collagenic and reticulum fibers, in which endothelial cells, fibroblasts and numerous corpora arenacea were embedded.

W. SAPHIR.

PARTIAL CONGENITAL ABSENCE OF THE PANCREAS. CHRISTLIEB, Virchows Arch. f. path. Anat. **289**:241, 1933.

The author adds one to the small number of reported cases of congenital partial absence of the pancreas. The patient was a woman who died at the age of 69 of cerebral hemorrhage. On the day before death the urine contained a trace of sugar. Sugar had not been present when she was under treatment for pneumonia a year and a half before death. The pancreas measured 8 by 4 by 1.5 cm. and was closely attached in the concavity of the duodenum. It consisted of a small head, an uncinate process and a small part of the body. Histologically, the islets were numerous and large, a condition interpreted as compensatory. The anomaly is ascribed to failure of development of the dorsal anlage of the pancreas.

O. T. SCHULTZ.

CONGENITAL ATRESIA OF THE LARYNX. E. FRITZ, Virchows Arch. f. path. Anat. **289**:264, 1933.

The anomaly described occurred in a new-born male infant 43 cm. in length. Heart tones were heard for from twelve to fifteen minutes after birth; the application of cold water led to a single spasmodic attempt at respiration. The larynx

appeared normal externally, and the epiglottis was normal. The superior opening of the larynx was normal, but at a distance of 0.5 cm. below the opening the larynx was closed. The trachea was absent for a distance of 3 cm. below the larynx. The bronchi and a portion of the trachea 1.5 cm. long, superior to the bifurcation, were normally formed. A narrow fistula connected the esophagus with the lower portion of the trachea. The generalized edema and hypertrophy of the lungs that previous observers have noted in atresia of the larynx were apparently not present in this instance.

O. T. SCHULTZ.

ANATOMIC STUDY OF THE ESOPHAGEAL HIATUS OF THE DIAPHRAGM. R. NEUMANN, Virchows Arch. f. path. Anat. **289**:270, 1933.

This is an anatomic study of the esophagus and stomach in the region of the diaphragmatic hiatus through which the esophagus passes, undertaken because of the clinical importance recently attached to so-called insufficiency and hernia of the hiatus. In 250 unselected necropsies the region of the hiatus was studied by a technic devised to permit examination without injury to any of the attachments of the diaphragm. In 100 necropsies anatomic dissections of the region were made. The mechanics of the region was studied by traction of the esophagus and by filling the esophagus and stomach. The hiatus is bounded by muscular and musculotendinous tissue and is filled in by finely fibrillated elastic connective tissue that is covered superiorly by the pericardium and pleura and inferiorly by the peritoneum. The cardiac antrum is bounded cephalad by the hiatic sulcus and caudad by the cardiac or Arnold's sulcus. The cardiac antrum is neither anatomically nor physiologically a part of either the esophagus or the stomach. The gastric mucosa ceased at Arnold's sulcus in 53 per cent of the bodies examined; in 4 per cent it extended upward to the hiatic sulcus. Traction and filling revealed the presence of bulbous enlargements, termed "bulbi oesophagi" if situated superior to the hiatic sulcus and "bulbi antri cardiaci" if situated inferior to this sulcus. The bulbous enlargements varied in size from that of a walnut to that of an egg. They were present in 12.5 per cent of the bodies examined. No correlation was noted between the clinical or constitutional state and the presence of bulbous enlargements, except that every person with a short, thick habitus associated with emphysema and cachexia had a bulbous cardiac antrum. The bulbous enlargements were not true hernias. They were not associated clinically with the gastrocardiac symptom complex of Roemheld or the epiphrenic syndrome of von Bergmann. Their formation is physiologic and is due to changes in the elasticity of the tissue of the hiatus, increase in the negative intrapleural pressure and increase in the size of the hiatus.

O. T. SCHULTZ.

ACQUIRED DIAPHRAGMATIC HERNIA OF THE STOMACH. G. JUNGFER, Virchows Arch. f. path. Anat. **289**:463, 1933.

Jungfer describes a hernia of the stomach through an enlarged esophageal foramen into the left pleural cavity. The esophagus was short. The course of the blood vessels led him to conclude that the hernia was not congenital but had developed after birth.

O. T. SCHULTZ.

LYMPHOGRANULOMATOSIS OF THE UTERUS. M. UDDSTRÖMER, Virchows Arch. f. path. Anat. **289**:486, 1933.

Uddströmer collected all the instances of lymphogranulomatosis reported in Sweden between 1915 and 1931 in which the diagnosis was confirmed by histologic examination. Involvement of the pelvic organs by direct continuity from pelvic lymph nodes is not unusual. His material included a case, which he describes, in which the involvement of the uterus was diffuse, did not extend beyond the limits of the organ and was apparently of hematogenous origin. O. T. SCHULTZ.

ARTERIAL DISEASE IN TYPHOID FEVER. Z. A. GASTEWA, Virchows Arch. f. path. Anat. **289**:636, 1933.

Gastewa presents two cases of typhoid fever, in one of which there was gangrene of the right foot, and in the other gangrene of both lower extremities and one upper extremity and terminal hemiplegia. Both patients were young persons, aged 15 and 21 years, respectively; hence senile vascular changes are to be excluded. The gangrene developed at the height of the disease, on the thirty-ninth day in the first case, during a relapse, and on the fourteenth day in the second case. Gangrene and hemiplegia were due to arterial thrombosis. In severe cases of typhoid fever the large and medium-sized arteries present localized areas of degeneration of the elastic tissue and necrosis of the connective tissue of the intima. The intimal changes may lead to thrombosis, which is the cause of the gangrene that sometimes complicates typhoid fever. The degenerative lesions of the arterial wall may be associated with tears into the media and through the wall.

O. T. SCHULTZ.

PERIOSTEAL BONE FORMATION AT THE EPIPHYSEAL LINE IN A CASE OF CONGENITAL SYPHILIS. G. GERSTEL, Virchows Arch. f. path. Anat. **289**:516, 1933.

Roentgenologic and anatomic examination of the lower end of each femur of a child who died at the age of 7 weeks of congenital syphilis revealed the presence of osseous outgrowths at the epiphyseal line. The bony masses had been formed by and within the thickened periosteum. The unusual lesion is interpreted as a regenerative reactive process evoked by the destructive osteochondritis that was present at the junction of the diaphysis and epiphysis. Spirochetes could not be demonstrated in the tissues; the patient had been under antisyphilitic treatment before death.

O. T. SCHULTZ.

HISTOLOGIC CHANGES IN THE CLINICALLY UNALTERED SKIN IN SYPHILIS. HELENE HERZENBERG, E. BANJAMOWITSCH and A. LEWIN, Virchows Arch. f. path. Anat. **289**:688, 1933.

Other observers have noted previously cellular proliferative reactions about the small blood vessels of the apparently normal skin of persons with syphilis. Although most of these observers considered the reaction nonspecific, Lukomski, in 1929, held it to be inflammatory and specific. Stadler accepted this view and attached great etiologic importance to the reaction in cardiovascular syphilis. Herzenberg, Banjamowitsch and Lewin examined histologically the macroscopically unaltered skin of thirty-four patients with syphilis in various stages. They observed a histiocytic proliferative reaction about the small vessels. But they also observed an identical reaction in the skin of a group of patients with diseases of the genito-urinary tract and of patients who had undergone operations and in the skin removed at necropsy from thirty subjects without syphilis. They interpret the reaction as hyperplasia of the perivascular connective tissue brought about by metabolic changes in the skin. It is not inflammatory in origin and has nothing to do with syphilis.

O. T. SCHULTZ.

THE PATHOGENESIS OF EPIPLOITIS. P. E. A. NYLANDER, Arb. a. d. path. Inst. d. Univ. Helsingfors **7**:1, 1933.

Two cases of omental inflammation are reported. In one a splinter of wood had perforated the gastro-intestinal tract and provoked a chronic inflammation of the omentum, with numerous giant cells. In the second case there was a chronic inflammatory swelling of the omentum, which was adherent to the transverse colon, probably as a result of a previous laparotomy. A variety of factors may cause omental inflammation, among which are previous operations, foreign bodies (fish bones, needles) and gastro-intestinal parasites, such as Taenia, Oxyuris and Distoma hepaticum.

JACOB KLEIN.

Microbiology and Parasitology

THE PROGNOSIS IN GONOCOCCAL ENDOCARDITIS. ALBERT B. NEWMAN. Am. Heart J. **8**:821, 1933.

Gonococcic endocarditis does not necessarily carry with it a fatal outcome. The literature on cases in which recovery was reported to have occurred is reviewed in detail. A case of postabortal gonococcic sepsis with gonococcic endocarditis and peripheral embolic phenomena, focal glomerulonephritis and valvular insufficiency which developed under observation and in which the patient underwent spontaneous recovery is reported.

AUTHOR'S SUMMARY.

GONOCOCCAL ENDOCARDITIS. W. W. BRANDES, Am. J. Dis. Child. **46**:341, 1933.

A case of gonococcal endocarditis of the tricuspid valve in an infant 10 days old is reported. In all probability, the endocarditis was secondary to gonorrheal conjunctivitis. There was an associated patent ductus arteriosus, which may have been associated with the development and localization of the lesion. The child in this case is the youngest patient having gonococcic endocarditis reported. A report of endocarditis secondary to conjunctivitis could not be found in the literature.

AUTHOR'S SUMMARY.

GONOCOCCIC MENINGITIS IN A NEW-BORN INFANT. W. L. BRADFORD and H. W. KELLEY, Am. J. Dis. Child. **46**:543, 1933.

In a new-born infant normally delivered from a mother with gonococcic cervicitis ophthalmia neonatorum developed on the second day. On the sixth day, generalized illness occurred, including fretfulness, fever, refusal of food and swelling and redness of the joints. On the eighteenth day, a diagnosis of purulent meningitis was established. From the spinal fluid an organism was isolated in pure culture which on further study gave the morphologic, cultural, fermentative and agglutinating characteristics of the gonococcus. The infant died on the forty-first day, and autopsy revealed purulent meningitis. The same organism was isolated from the meningeal exudate. In view of the clinical and bacteriologic evidence, a diagnosis of gonococcic meningitis seems justified.

AUTHORS' SUMMARY.

CULTURE OF THE TUBERCLE BACILLUS BY THE LÖWENSTEIN METHOD. C. W. LAYMON, Arch. Dermat. & Syph. **28**:35, 1933.

Laymon cultured tubercle bacilli on Löwenstein's, Korper's and Dorset's mediums and concluded that Löwenstein's medium was superior to the other two. One hundred and forty specimens of blood from thirty-five patients with tuberculosis, tuberculids, lupus erythematosus, erythema induratum, erythema nodosum and erythema multiforme were cultured according to Löwenstein's method and on his medium. All the cultures were negative. Laymon emphasizes the difficulties of the procedure, the expense involved and the time required. He is unable to explain the entirely negative results.

S. W. BECKER.

SPOROTRICHOTIC CHANCRE. H. S. CAMPBELL, K. FROST and O. A. PLUNKETT, Arch. Dermat. & Syph. **28**:61, 1933.

A small lesion over the dorsum of the distal interphalangeal joint following a scratch healed slowly and then broke down and remained for five months. Cultures of the seropus on Sabouraud's medium gave no growth. Some of the tissue placed on Sabouraud's medium gave a growth of Sporotrichum. The organism was inoculated intraperitoneally and subcutaneously in several rats and guinea-pigs, and in only one rat could it be recovered from a subcutaneous lesion. The authors emphasize the difficulty of recovering Sporotrichum from some lesions.

S. W. BECKER.

FOCAL CELL REACTIONS IN TUBERCULOSIS AND ALLIED DISEASES. THEOBALD SMITH, Bull. Johns Hopkins Hosp. **53**:197, 1933.

"The idea presented in the foregoing pages is the stimulating activities of the tubercle bacillus. This may manifest itself in many grades of intensity, leading to the development of epithelioid cells, giant cells, the stimulation of fibroblasts, and possibly the direct production of necrosis in high concentration. The epithelioid cell is not related to the macrophage either as to origin or function. It is formed locally through contact of its progenitors with parasites or their products. It differs in these respects from polymorphs which are frankly phagocytic. Their activity amounts to a protection of the host generally, whereas the progenitors of the epithelioid and foreign body giant cells tend to perform this function locally. This idea is in contrast with the concept of phagocytosis which postulates prompt specific aggressiveness on the part of tissue cells. The idea implies, moreover, that immunity tends towards lesser and lesser susceptibility on the part of the cells instead of greater activity, and ending finally in the feeblest reaction of the foreign body giant cell. The change following primary infection as manifested in secondary foci is assumed to be associated with antigenic and antibody products discharged from the primary foci which act upon the bacilli in transit and prepare the reticulo-endothelial cells for the secondary encounter. Finally it should be emphasized that differences in the histological structure of tuberculous lesions appearing more or less regularly may imply different races of bacilli as well as genetic or acquired differences in the resistance of individuals of the host species. A study of such variations among tubercle bacilli is still in its beginnings."

LYMPHOGRANULOMA INGUINALE. H. M. COLE, J. A. M. A. **101**:1069, 1933.

Lymphogranuloma inguinale is a distinct granulomatous entity involving the lymph nodes and is generally venereal in origin. After incubation for from one to several weeks, and not necessarily manifested by a primary sore, the disease results in the formation of a chronic bubo which eventually suppurates. In the female and rarely in the male the lymph nodes around the lower portion of the rectum may be involved, the inflammatory reaction often resulting in stricture of the rectum. Occasionally in the female there may be involvement of the lower part of the vaginal wall and of the labia in the form of a chronic ulcerative elephantiasis —esthiomene. The cause of lymphogranuloma inguinale is a filtrable virus which can be transferred to several of the lower animals (monkeys, rabbits, white mice, guinea-pigs). A specific diagnostic cutaneous reaction (Frei reaction) has been evolved, an emulsion of material from unbroken involved nodes being used as the antigen. A series of positive Frei reactions were obtained in patients suspected of having had the disease in the past. Among them were two who had buboes thirty years before, and one who had a bubo between thirty and forty years before. This allergy of the skin apparently persists through life. Thirty-seven persons with lymphogranuloma inguinale and bubo formation, as well as two with esthiomene and thirteen with anorectal symptoms and stricture of the rectal wall, gave positive Frei reactions and many had no history or signs of syphilis or of tuberculosis.

FROM AUTHOR'S SUMMARY.

LYMPHOMATOSIS, MYELOMATOSIS AND ENDOTHELIOMA OF CHICKENS CAUSED BY A FILTERABLE AGENT. J. FURTH, J. Exper. Med. **58**:253, 1933.

A new transmissible strain of leukosis of chickens is described that causes (*a*) lymphomatosis with or without formation of tumors and with or without leukemia, (*b*) myelocytomatosis with or without leukemia and (*c*) endothelioma. All these diseases are transmissible by material free from viable cells, and the available evidence indicates that they are caused by a single filtrable agent.

AUTHOR'S SUMMARY.

CORYZA OF THE DOMESTIC FOWL. J. B. NELSON, J. Exper. Med. **58**:289 and 297, 1933.

By a method combining filtration and cultivation, an unidentified gram-negative bacillus was isolated from the nasal exudate of fowl experimentally infected with an uncomplicated coryza. Isolation was accomplished by cultivation of the nasal exudate on sealed blood agar plates after unsuccessful attempts to produce colonies on open plates. Injection of the organism into the palatine cleft of a normal bird was regularly followed by an inflammation of the nasal mucosa and a discharge from the nares. A para-influenza bacillus which was also recovered from the nasal tracts of affected fowl was innocuous. Certain cultural characters of the bacillus, bearing on its classification, are discussed.

Three types of an uncomplicated fowl coryza, differing in onset and duration of symptoms, developed after nasal exudate from fowl naturally infected was injected intranasally into normal birds. With two of the types protection tests were carried out in an attempt to explain why the "bacilliary" disease regularly ran a shorter course than the "exudate" disease. Reciprocal protection was demonstrated in one case, but in the other the birds which had recovered from the "bacilliary" disease were susceptible to reinfection from the exudate. There was no indication, however, that a second infectious agent was present in the exudate, and the failure to cross-immunize was ascribed, rather, to a reduction in the immunizing properties of the specific bacillus induced by artificial cultivation. It was also noted that the coryzas produced by injection of exudate and bacilli, respectively, could be transmitted from infected birds to normal ones by direct contact. In both cases one bird out of five failed to contract coryza on exposure. When the respective agents to which these two birds had been exposed were later injected into them, the birds were found to be resistant.

AUTHOR'S SUMMARIES.

THE EFFECT OF A PRIMARY INFECTION ON CONTACT TUBERCULOSIS IN RABBITS. M. B. LURIE, J. Exper. Med. **58**:305, 1933.

Seventy-three per cent of normal rabbits exposed for about one year to cage mates infected with tubercle bacilli of bovine type acquired respiratory or alimentary tuberculosis, which was fatal in 50 per cent of the cases; 63.6 per cent contracted tuberculosis during the first six months. Of rabbits vaccinated with tubercle bacilli of human type and exposed in the same cages at the same time, only 36.8 per cent acquired tuberculosis during the first six months. Later this resistance waned, and by the end of the year altogether 60 per cent had contracted tuberculosis, of which 38 per cent succumbed. The disease in the vaccinated rabbits was shown to be of exogenous origin by the isolation in pure culture from the same rabbit of the human type of bacillus from the primary infection, and of the bovine type of bacillus from the naturally acquired lesion. The vaccination reduced the incidence, extent and mortality of the disease, affected the route of infection, changed its pathologic character, and retarded its progress. The disease acquired by vaccinated rabbits shared many characteristics with the type of tuberculosis found in adult human beings. It is suggested that this method may be used with relative ease in studying many phases of naturally acquired tuberculosis in small laboratory animals.

AUTHOR'S SUMMARY.

THE PARTICULATE NATURE OF THE BACTERIOPHAGE. R. F. FEEMSTER and W. F. WELLS, J. Exper. Med. **58**:385, 1933.

Experimental evidence is brought forward to show that the bacteriophage obeys very closely the laws of chance distribution of particles in suspension.

AUTHORS' SUMMARY.

PSEUDORABIES (INFECTIOUS, BULBAR PARALYSIS, MAD ITCH). E. W. HURST, J. Exper. Med. **58**:415, 1933.

The histologic aspects of pseudorabies differ materially in various animal species. In the rabbit, subcutaneous, intradermal or intramuscular inoculation leads to local inflammation and necrosis. The infection ascends the peripheral nerves (possibly both interstitially and by the axis-cylinders) to the corresponding spinal ganglions and segments of the spinal cord, where primary degeneration of nerve and glial cells takes place. The nerve cell changes are probably responsible for the cardinal symptom of the disease, itching. Death ensues soon after the virus reaches the medulla, before visible changes have been produced there. Intracerebral inoculation is followed by characteristic lesions in the meninges, in subpial glial cells and in superficially placed nerve cells. Morbid changes in the lungs are not necessarily related to the presence of the virus, but specific lesions may be present. Intranuclear inclusions bearing some resemblance to those seen in herpetic encephalitis, yellow fever, etc., occur in cells derived from all embryonic layers. The disease in the guinea-pig resembles closely that in the rabbit and is modified only by the slightly greater resistance of the guinea-pig. In the monkey, after intracerebral inoculation, widespread degeneration and necrosis of cortical nerve cells occur and are accompanied by specific nuclear alterations in nerve and glial cells but not in cells of mesodermal origin. No lesions are found in other viscera. In the spontaneous disease in the cow the lesions approximate those in the monkey more closely than those in the rabbit. In the pig, vascular and interstitial lesions predominate, degeneration of nerve cells is relatively slight and typical inclusions are not observed. These differences probably explain the benign course of the malady following subcutaneous inoculation in this animal. The lymphatic system also participates in the reaction to the virus. AUTHOR'S SUMMARY.

INTRANASAL VIRULENCE OF PNEUMOCOCCI FOR MICE. L. T. WEBSTER and A. D. CLOW, J. Exper. Med. **58**:465, 1933.

Smooth colony pneumococci freshly isolated from human beings and instilled in small doses into the nasal passages of special mice raised under standard conditions brought about a characteristic infection, and this spread to healthy contacts, inciting in them either a fatal infection or development of the carrier state. Differences in the response of individual hosts to the same dose of a given culture ranged from a completely refractory or nasopharyngeal carrier state, or a local cervical lymphadenitis, to fatal lobular or lobar pneumonia with or without pleurisy, empyema and pericarditis, and acute fatal septicemia. The pneumococci exhibited consistent individual strain differences with respect to ability to infect when instilled intranasally into mice, and also differences in spread to contacts. Degree of intranasal virulence paralleled demonstrable ability to spread to contacts. Degree of intranasal virulence of strains did not parallel degree of intraperitoneal virulence in 50 per cent of the strains—high intranasal virulence was accompanied by either high or moderate intraperitoneal virulence, and low intranasal virulence by high, moderate, or low intraperitoneal virulence. Type III strains were of relatively high intranasal and intraperitoneal virulence; type II strains were mostly of low intranasal but of high or moderate intraperitoneal virulence. Most strains of other types were of low intranasal as well as low intraperitoneal virulence. The intranasal virulence of the pneumococci was not enhanced by passage through animals. Nasal passage reduced the intranasal virulence to zero but did not affect the intraperitoneal virulence, form of colony and agglutinative specificity. Intraperitoneal passage maintained the characteristic level of the intranasal virulence for a period, increased the intraperitoneal virulence in some instances, but did not affect the form of colony or the agglutinative properties. AUTHORS' SUMMARY.

THE FIBRINOLYTIC ACTIVITY OF HEMOLYTIC STREPTOCOCCI. W. S. TILLETT and R. L. GARNER, J. Exper. Med. **58**:485, 1933.

Broth cultures of hemolytic streptococci derived from patients are capable of rapidly liquefying normal human fibrin clot. The active fibrinolytic principle is also contained in sterile cell-free filtrates of broth cultures. The degree of activity of the filtrates parallels the activity of the whole broth cultures sufficiently closely to indicate that large amounts of the fibrinolytic substance are freely excreted into the surrounding medium and pass readily through Berkefeld V, Seitz and Chamberland filters. The occurrence of fibrinolysis is most strikingly observed when plasma or fibrinogen is mixed with active cultural material before the formation of the clot is effected. Under the standard experimental conditions described, complete dissolution of human plasma clot (whole oxalated plasma plus calcium chloride) occurs in about ten minutes; complete dissolution of human fibrinogen clot (chemically isolated fibrinogen minus the thrombin) takes place in about two minutes. Titrations of the activity of the filtrates are recorded in table 4 in the article. Twenty-eight strains of Streptococcus haemolyticus isolated from patients suffering from various manifestations of streptococcic infection have been tested for capacity to liquefy fibrin clot. Broth cultures of all the strains induced fibrinolysis. Of eighteen strains of Str. haemolyticus of animal origin, only three were capable of causing dissolution of fibrin clot. Completely negative results were obtained with thirty-eight strains of other bacterial species. The plasma of many patients who had recovered from acute infections with hemolytic streptococci, when clotted in the presence of active cultures, was highly resistant to fibrinolysis. Furthermore, serum derived from patients whose plasma clot was resistant often conferred on normal plasma clot an antifibrinolytic property. One example of the resistance possessed by the blood of convalescent patients is presented in this report. A second article, now in preparation, will give in detail a large number of observations on the relation of infection to the development of resistance to the fibrinolytic activity of hemolytic streptococci. In contrast to the susceptibility of normal human fibrin clot, rabbit fibrin clot is totally resistant to dissolution when tested under comparable conditions. The insusceptibility of rabbit fibrin clot is manifest provided the coagulum is composed of rabbit constituents. When human thrombin is used to clot rabbit plasma or fibrinogen in the presence of active cultures, fibrinolysis is not prohibited. The rôle of thrombin in determining the resistance or susceptibility of rabbit fibrin to dissolution offers a suggestive approach to problems relating to the underlying mechanism.

AUTHORS' SUMMARY.

THE RELATION OF VITAMIN C DEFICIENCY TO INTESTINAL TUBERCULOSIS IN THE GUINEA-PIG. M. MCCONKEY and D. T. SMITH, J. Exper. Med. **58**:503, 1933.

Seventy-two adult guinea-pigs were fed tuberculous sputum daily for periods ranging from six weeks to four months. Thirty-seven of these were maintained on a diet partially deficient in vitamin C; twenty-six acquired ulcerative intestinal tuberculosis. Of the remaining thirty-five animals, the diet of which was supplemented by an adequate amount of vitamin C, only two acquired tuberculous ulcers in the intestines. From these studies we conclude that the ingestion of tubercle bacilli is not the sole factor in the production of intestinal tuberculosis in the guinea-pig. In our opinion, an adequate supply of vitamin C usually protects the guinea-pig against ulcerative intestinal tuberculosis.

AUTHORS' SUMMARY.

THE TITRATION OF POLIOMYELITIC VIRUS CONTAINING TISSUE. M. BRODIE, J. Immunol. **25**:87, 1933.

Rhesus monkeys appear to have a uniform susceptibility to the virus of poliomyelitis and so it is possible to determine the minimal completely paralyzing dose (M. C. P. dose) for cord specimens. In passage of the virus through monkeys the infectivity of cord tissue varied from animal to animal; so, if experimental

results are to be compared, they must be expressed in terms of the M. C. P. dose of virus. Intracerebral inoculation of from 1 to 80 M. C. P. doses did not appear to influence the period of incubation or the course of the disease, but borderline infective doses prolonged both, while overwhelming amounts of virus shortened them. Subinfective intracerebral doses of the virus of poliomyelitis failed either to immunize animals or to render them more susceptible to the virus.

AUTHOR'S CONCLUSIONS.

FILTRABLE VIRUS CARRIERS. C. S. GIBBS, J. Infect. Dis. **53**:169, 1933.

Filtrable virus carriers are reported in hog cholera, rinderpest and infectious laryngotracheitis of poultry. This is the first instance in which filtrable virus carriers have been identified a priori by laboratory tests and not merely referred to as possibilities through reasoning a posteriori. Studies of this nature are important, for an exact knowledge of carriers is indispensable to any program for the control of disease.

AUTHOR'S SUMMARY.

TUBERCLE BACILLUS DISSOCIANTS AND VARIANTS. F. B. SEIBERT, E. R. LONG and N. MORLEY, J. Infect. Dis. **53**:175, 1933.

A typical avian tubercle bacillus (Van Es, 1921) grew in rough, dry colonies on Long's synthetic medium and in smooth, greasy colonies on Petroff's egg medium. The S bacilli were longer, more slender, more beaded and less acid-fast than the R bacilli, and tended to stratify, whereas the R bacilli piled up in irregular loose clumps. In the few experiments carried out, the S bacilli proved more virulent for hens than the R bacilli. Differences were conspicuous in the spleen. Soon after inoculation of the hens with S bacilli numerous minute tubercles formed, which were noncaseous and loaded with bacilli. In hens infected with R bacilli at the same time, tubercles were fewer, larger and caseous, with few visible bacilli. At a later period the lesions were more nearly alike, but more numerous in the hens infected with S bacilli. Chemically the S form of the avian bacillus differed from the R form in several respects. The S bacilli contained less water and more fatty material than the R bacilli, and the fatty extracts of the S bacilli possessed higher iodine numbers. Comparable chemical fractionations were made of two strains of tubercle bacilli of human type and of different virulence, H 37 and R 1, grown on both Long's synthetic medium and Petroff's egg medium. The appearance of the colonies did not differ on the two mediums, but characteristic chemical differences existed as in the case of the two visibly different forms of avian bacilli.

AUTHORS' SUMMARY.

MONILIASIS WITH MENINGEAL INVOLVEMENT. L. W. SMITH and M. E. SANO, J. Infect. Dis. **53**:187, 1933.

A case of moniliasis involving the meninges in an infant of 22 months is presented. Bacteriologic studies suggested that the organism is of the type of Monilia albicans although it presents certain minor cultural, fermentative and serologic variations. Experimental data show that the organism is highly pathogenic for rabbits and in these animals tends to have a curious and unusual neuropathic affinity, producing invariably, on intravenous inoculation, definite meningitis as well as focal lesions in the brain. In this respect, the organism is much more virulent than the control strains, which less regularly produce involvement of the central nervous system.

AUTHORS' SUMMARY.

BACTERIOPHAGE OF BACILLUS PERTUSSIS. L. W. SAUER and L. HAMBRECHT, J. Infect. Dis. **53**:197, 1933.

The bacteriophage of Bacillus pertussis was produced by growing young cultures of old strains of B. pertussis in a concentrated fresh sewage bouillon which contained a small amount of defibrinated blood. Lysis was transmitted in series, and platings made from such lysed tubes gave evidence of plaques.

AUTHORS' SUMMARY.

MICROMOTION PICTURES OF THE GROWTH OF MYCOBACTERIUM PHLEI. R. W. G. WYCOFF and K. C. SMITHBURN, J. Infect. Dis. **53**:201, 1933.

Micromotion pictures have been made of the development of the timothy grass bacillus, Mycobacterium phlei, on solid mediums. In the phase of active growth the bacteria are rods which multiply only by transverse fission. As they age, the rods fractionate into coccobacilli, many of which eventually round up into deeply staining acid-fast cocci. These cocci apparently represent a resting stage of the organism. On a fresh medium they (1) elongate into bacilli, (2) sprout into rods smaller in diameter than the spheres from which they spring or (3) through coccoid division produce smaller cocci that eventually become rods. There is no evidence that in M. phlei these growth changes are repetitively cyclic.

AUTHORS' SUMMARY.

GONOCOCCIC MENINGITIS. M. M. STRUMIA and J. J. KOHLHAS, J. Infect. Dis. **53**:212, 1933.

Involvement of the nervous system by gonococcic infection appears to be rare. There are in the literature only seven approved cases of gonococcic meningitis, including our own. In addition to these, ten other cases have been reported as cases of gonococcic meningitis in which that diagnosis is probably correct. Even if the seventeen cases are all accepted as authentic, they are too few to be treated statistically. All proved cases of gonococcic meningitis occurred in the course of acute gonorrheal infection or during acute exacerbation of chronic gonorrheal infection. Only two of the seventeen cases occurred in women. The ages of the patients were from 9 to 30 years, the majority of the cases occurring in patients between 18 and 23 years of age. In most of the instances, other and more common complications of gonorrheal urethritis occurred before, during or after the meningeal symptoms, such as prostatitis, cystitis, arthritis, endocarditis and cutaneous exanthem (purpura). In a few instances, however, the meningitic signs were the first to appear in addition to the urethritis. Such was the case in our patient. In all likelihood, the meningitis follows gonococcemia and is only an uncommon localization of a common generalized condition. In two of the seven proved cases the patients died, and in only one was an autopsy made. The postmortem observations were similar to those of meningococcic meningitis. If we include the probable but not proved cases, six of a total of seventeen terminated in death. The therapeutic measures employed appear to be of so varied a nature as to make their value doubtful. It can be stated, however, that repeated spinal punctures and drainage offer considerable relief from pain and discomfort. It appears to be worth while to make a careful bacteriologic study in cases of meningitis complicating acute gonorrheal urethritis.

AUTHORS' SUMMARY.

EFFECT OF FEEDING SALMONELLA ORGANISMS TO RATS. E. VERDER, E. DOWNING and H. W. WILCOX, J. Infect. Dis. **53**:245, 1933.

Living Salmonella aertrycke and Salmonella enteritidis, when eaten, caused diarrhea in varying percentages of white rats, both those on balanced diets and those on diets containing more than a normal amount of starch, sugar or protein. The symptoms rarely appeared in less than twenty-four hours after the feeding. They would seem, therefore, to result from the multiplication and probable rapid disintegration of the swallowed organisms.

AUTHORS' SUMMARY.

SALMONELLA FOOD POISONING. E. VERDER and C. SUTTON, J. Infect. Dis. **53**:262, 1933.

Two persons who had eaten heated custard cultures of a recently isolated strain of Salmonella enteritidis and five persons who had drunk heated or filtered washings from similar cultures did not become ill, though in one case the heated washings contained a few living organisms. Another person who ate a custard

culture of another enteritidis strain which had been insufficiently heated to kill many of the contained organisms became definitely ill, with diarrhea developing in twenty hours and marked prostration in thirty-six hours. Monkeys likewise became ill only when living organisms (S. enteritidis) were taken. Their symptoms were strikingly similar to those of human beings with food poisoning despite variations in the severity of the reactions and lack of uniformity in the positive results.

AUTHORS' SUMMARY.

RELATION OF SPIRAL ORGANISMS TO THE ROUGH COLONY OF BACTERIUM FUSIFORMIS. R. TUNNICLIFF, J. Infect. Dis. **53**:280, 1933.

This study of the colonies of Bacterium fusiforme shows that colonies containing the bacillary forms are smooth, and that the spiral organisms are dissociants of the fusiform bacillus, associated with its rough colony.

AUTHOR'S SUMMARY.

ROCKY MOUNTAIN SPOTTED FEVER AND BOUTONNEUSE FEVER. L. F. BADGER, Pub. Health Rep. **48**:507, 1933.

"Boutonneuse fever of the Mediterranean littoral, first described by Conor and Bruch, is an acute, noncontagious, febrile disease transmitted by the tick Rhipicephalus sanguineus and characterized clinically by fever, headaches, muscular and joint pains, and an exanthem." Brumpt concluded on immunologic grounds that boutonneuse fever and Rocky Mountain spotted fever are distinct entities. Badger's tests indicate that they are immunologically identical.

THE RELATIONSHIP BETWEEN ZOSTER AND VARICELLA AS SHOWN BY COMPLEMENT FIXATION. R. T. BRAIN, Brit. J. Exper. Path. **14**:67, 1933.

The serums of persons convalescent from herpes zoster and varicella contain specific antibodies, which can be demonstrated by complement fixation when the vesicle fluids are used as antigens. The vesicle fluid of herpes zoster gives equally good fixation in the presence of both herpes zoster and varicella antibodies, and the same is true of the vesicle fluid of varicella. These findings are in conformity with those of Netter and his colleagues. They indicate the close relationship and possible identity of the viruses of herpes zoster and varicella.

AUTHOR'S SUMMARY.

A VITAMIN NECESSARY FOR THE GROWTH OF B. SPOROGENES. C. J. G. KNIGHT and P. FILDES, Brit. J. Exper. Path. **14**:112, 1933.

A factor, comparable to a vitamin, necessary for the growth of Clostridium sporogenes is described. Its chemical nature is indicated. Evidence is brought forward to suggest that this vitamin may be closely allied to other factors which have been described as affecting the growth of plants and other forms of life.

AUTHORS' SUMMARY.

NUCLEAR INCLUSIONS IN THE LIVER IN RIFT VALLEY FEVER. G. M. FINDLAY, Brit. J. Exper. Path. **14**:207, 1933.

Intranuclear acidophilic inclusions have been found in the hepatic cells of the sheep, goat, rhesus monkey, marmoset, rat, mouse, field vole, wood vole, golden hamster and gray squirrel infected with Rift Valley fever. The inclusions develop in the nucleoplasm of the hepatic cells and are visible in fresh preparations. The inclusions do not give a reaction for fats, thymonucleic acid or masked iron. Their development coincides with a margination of the nuclear chromatin on the nuclear membrane, which eventually ruptures. The morphologic and tinctorial properties of the inclusions are described and compared with those associated with other viruses that give rise to inclusions in the nuclei of the cells of the liver. The lysis of mitochondria and the disruption of the Golgi apparatus in the cells of the liver in Rift Valley fever are also described.

AUTHOR'S SUMMARY.

VARIATION IN STOCK CULTURES OF MENINGOCOCCI. B. G. MAEGRAITH, Brit. J. Exper. Path. **14**:219 and 227, 1933.

Great variation in agglutination by "type" serums occurs among single colonies of stock meningococci. Littledale (type I) strains show a tendency to overlap into type III to such an extent that these types appear to be approaching interchangeability. There is little evidence of a division of group and specific antigens among single colonies derived from stock type cultures. The so-called types I and III of the meningococcus are in all probability not fixed types.

Certain variants of stock strains of meningococci can be detected by the characteristics of their growth on homologous immune serum agar. One variant develops haloes in this medium and the other does not. Investigation of the properties of these variants has indicated that they are of "smooth" and "rough" nature, respectively. This is supported by their differences in growth in various mediums, in their fermentation and precipitin reactions and in their effects on guinea-pigs. Agglutination and absorption reactions with serums prepared from the variants do not agree with the results obtained by Enders with his "S" and "R" forms. A tentative explanation of this discrepancy is offered. These variants are being further investigated.

AUTHOR'S SUMMARIES.

THE SIZE OF THE VIRUS OF FOWL PLAGUE ESTIMATED BY ULTRA-FILTRATION. W. J. ELFORD and C. TODD, Brit. J. Exper. Path. **14**:240, 1933.

The diameter of the elementary particles of the virus of fowl plague as they exist in the body fluids of the fowl has been estimated by analytic ultrafiltration through graded collodion membranes to be from 60 to 90 microns. Control experiments in which Staphylococcus K bacteriophage (size, from 50 to 75 microns) was admixed with a suspension of the virus confirmed the close relationship in size between the particles of this phage and those of the virus. Differentiation of their filtrabilities was only just possible.

AUTHORS' SUMMARY.

DEVELOPMENTAL FORMS OF THE VIRUS OF PSITTACOSIS. S. P. BEDSON, Brit J. Exper. Path. **14**:267, 1933.

Evidence has been produced to show that the forms described in the early stages of infection of the mouse with psittacosis are developmental stages of the virus. The virulence of the virus in the form of plaques or primary morulae is considerably less than that of the elementary bodies. The large or intermediate forms filter less readily than the elementary bodies, but the latter are thrown down more readily by centrifugation. It would appear that the virus of psittacosis produces inclusions, though not the fully developed acidophil inclusions characteristic of many viruses. It has been found impossible to say whether the plaque is homogeneous—a plasmodium—or an aggregate of virus particles the detail of which is obscured by inclusion material.

AUTHOR'S SUMMARY.

THE FILTRATION OF SPIROCHAETES THROUGH GRADED COLLODION MEMBRANES. E. HINDLE and W. J. ELFORD, J. Path. & Bact. **37**:9, 1933.

Filtration experiments in which graded collodion membranes were used showed that the limiting porosity for Spirochaeta biflexa is one in which the pores measure 0.25 micron and that the porosity for Spirochaeta pallida is one in which the pores measure approximately 0.4 micron. This is interpreted as indicating a diameter of 0.1 micron for the former and a diameter of 0.2 micron for the latter. The corresponding figures obtained from photographs made by the method in which an ultraviolet ray background is used were approximately 0.11 and 0.33 micron. The spirochetes passed readily through the membranes. This method furnishes a simple and effective means of separating spirochetes, including S. pallida, from other organisms. No evidence was obtained of the existence of a special filtrable phase with a diameter significantly smaller than that of the spirochete.

AUTHORS' SUMMARY.

Immunology

A Diagnostic Test for Infectious Mononucleosis. W. W. Bunnell, Am. J. M. Sc. **186**:346, 1933.

We have employed the sheep cell agglutinin test in over two thousand cases representing seventy-six clinical conditions. With the exception previously noted, namely, serum disease, we have been unable to demonstrate an appreciable increase of heterophile agglutinins for sheep cells in the serums above the normal dilution of 1:8. In fifteen cases of infectious mononucleosis we have found a consistent increase in all the cases. The titers, ranging from 1:64 to 1:4,096, apparently depended to a considerable extent on the stage of the disease at which the serum was obtained and on the severity of the illness. None of the common conditions manifesting a similar clinical picture, such as acute adenitis, tuberculous or syphilitic adenitis, Hodgkin's disease, acute or chronic lymphatic or myelogenous leukemia, aplastic anemia, purpura haemorrhagica, agranulocytic angina or Vincent's angina, has shown an increase in heterophile agglutinin titer. In view of these observations it seems justifiable to accept the test for heterophile agglutinins for sheep cells as a valuable diagnostic procedure in differentiating infectious mononucleosis from a number of clinical conditions of a far more serious nature. Cases presenting a suggestive clinical and serologic picture and blood serum with an agglutination for sheep cells in a dilution of at least 1:64 can apparently safely be diagnosed as infectious mononucleosis and a favorable prognosis given.

Author's Summary.

The Comparative Sensitiveness of the Pirquet and the Intracutaneous Tuberculin Tests. J. D. Aronson, D. Zacks and J. J. Poutas, Am. Rev. Tuberc. **27**:465, 1933.

Two large groups of white persons near Boston were tested simultaneously by both methods. An average of 2.9 per cent of a group of children between the ages of 5 and 19 years who failed to react to the Pirquet test reacted to 0.01 mg. of tuberculin. When 1 mg. was employed, the percentage of those who failed to react to the Pirquet test but reacted to the intracutaneous test averaged 19.1. The total number of those who reacted to the intracutaneous test and not to the Pirquet test revealed a negligible increase in the amount of infection detected by this means. Repetition of the Pirquet test yielded a negligible increase. A mathematical factor, a "correction figure," could not be devised to convert results by the one method into those obtained by the other. The intracutaneous test can be carried out as expeditiously as the Pirquet test. The intracutaneous tuberculin test is more sensitive than the Pirquet test in determining the incidence of tuberculous infection. Results obtained by the two methods are not directly comparable.

H. J. Corper.

The Persistence of Immunity after the Abolition of Allergy by Desensitization. A. R. Rich, F. B. Jennings, Jr., and L. M. Downing, Bull. Johns Hopkins Hosp. **53**:172, 1933.

Rich and his associates carried out experiments on Pasteurella aviseptica and pneumococcic infection in order to determine whether immunity would be less efficient after the abolition of allergy by desensitization. When the capacity for reacting with allergic inflammation is completely destroyed by the injection of large doses of killed bacteria into the veins of hypersensitive, immune animals, immunity to intracutaneous infection with millions of lethal doses of living virulent bacteria remains intact. Inflammation at the site of infection in such animals is far less than in untreated allergic, immune animals—far less, indeed, than in normal controls; but the bacteria are prevented from spreading from the site and are as effectively destroyed as in the allergic, immune body. The immune state so greatly enhances the protective power of the inflammatory mechanism that much

less, rather than much more, inflammation is required to protect the body from infection. Damage to the tissue at the site of infection is also far less in desensitized animals than in allergic ones. Even in the highly allergic, immune body, therefore, allergic inflammation is not necessary for protection against infection, and in its absence the body is protected with much less damage to the tissue than that which occurs in the allergic body.

AUTHORS' SUMMARY.

PNEUMOCOCCUS AUTOLYSATES IN DERMAL INFECTION IN RABBIT. K. GOODNER, J. Exper. Med. **58**:153, 1933.

In dermal infections caused by the pneumococcus in rabbits, the addition of pneumococcus autolysate to an infective inoculum favors the invasiveness of the particular strain employed but does not alter the kind of virulence possessed by that strain. Autolysates exhibiting this enhancing property also induce purpura in mice and inhibit the coagulation of blood in rabbits. The relation of these properties to the infectivity of the pneumococcus and the possible rôle of bacterial autolysis in natural infection are discussed.

AUTHOR'S SUMMARY.

SPREADING BACTERIAL FACTOR. F. DURAN-REYNALS, J. Exper. Med. **58**:161, 1933.

Invasive strains of staphylococci and streptococci contain a soluble factor which markedly increases the permeability of tissue and enhances the infections produced by these organisms, by other bacteria and by vaccine virus as well. The non-evasive strains of the same species of staphylococci and streptococci do not contain this factor. The enhancing substance elaborated locally by organisms passes into the circulating blood and may enhance local infections elsewhere by bringing about a general increase of the permeability of tissues. In the phenomena it elicits, the factor is similar to the spreading factor extracted from many animal tissues, especially from the testicle.

AUTHOR'S SUMMARY.

RESISTANCE TO PNEUMOCOCCUS INFECTION IN RABBITS. K. GOODNER and E. G. STILLMAN, J. Exper. Med. **58**:183 and 195, 1933.

The dermal pneumococcic infection was employed to determine the active resistance of rabbits against infection, and an evaluating scale of the gradient of resistance was established. The significance of the various degrees of resistance is discussed, and the possible general inferences of the observations are indicated.

The degree and duration of the active resistance against pneumococcic infection were determined in rabbits which received intravenous injections of a heat-killed suspension of pneumococci of the three principal types. The resistance induced by the immunization procedure varied in degree and in duration with each type of pneumococcus.

AUTHORS' SUMMARY.

VACCINATION WITH HEAT-KILLED AND FORMALDEHYDIZED TUBERCLE BACILLI. R. M. THOMAS, J. Exper. Med. **58**:227, 1933.

Rabbits vaccinated with tubercle bacilli killed by exposure to a solution of formaldehyde (0.4 per cent) did not show any acquired resistance to subsequent infection with bovine tubercle bacilli, while rabbits vaccinated with tubercle bacilli which had been killed by heating to 70 C. for one hour survived more than half as long again as their controls. Intraperitoneal injection of either the formaldehyde-killed or the heat-killed vaccine into guinea-pigs made them skin-sensitive to human tubercle bacillus protein. The rate of absorption of the formaldehyde-killed vaccine when introduced beneath the skin was similar to that of the heat-killed vaccine. Following the intravenous injection of heat-killed tubercle bacilli, it was found that a massive tuberculous pneumonia developed in rabbits. A study of the production and ultimate absorption of the cellular exudate showed that these processes were

similar to those found after the injection of living bacilli. The lesions which followed the injection of heat-killed bacilli differed from the lesions found in active tuberculosis in that in any one animal they showed a striking uniformity of appearance, while in the active disease the lungs showed a great diversity in type of lesion. Studies of the blood cells during the period of injection of dead organisms showed that the changes which are characteristic of the period during which a tuberculous pneumonia develops in rabbits (from thirty to forty days after inoculation) were faithfully reproduced. It is suggested that the process of regression described may be similar to that which occurs in tuberculosis of childhood, in which rather extensive pulmonary lesions resolve without leaving evidence of damage to the parenchyma of the lung.

AUTHOR'S SUMMARY.

EFFECT OF NONSPECIFIC AGENTS ON ACTION OF ANTIPNEUMOCOCCUS SERUM. A. G. GELARIE and A. B. SABIN, J. Exper. Med. **58**:237, 1933.

Gelarie and Sabin attempted to determine whether or not nonspecific agents are capable of exerting any influence on the response of animals infected with the pneumococcus to specific serum therapy. They demonstrated that whereas gold (empirically chosen) by itself had very little effect on either the course or the outcome of the experimental pneumococcic infection, it is nevertheless capable of exerting a definite and marked beneficial effect in rabbits treated with a subeffective dose of the specific antiserum. Of the rabbits treated with the subeffective dose of serum alone 71 per cent died and only 29 per cent survived. The additional administration of gold reversed this ratio with the result that in a large group of rabbits which received the combined therapy, 77 per cent survived and only 23 per cent died.

AUTHORS' SUMMARY.

CHANGES IN THE TITER OF ANTI-PNEUMOCOCCAL HUMORAL IMMUNITY IN ADULT HUMAN BEINGS. J. B. GRAESER and M. C. HARRISON, J. Exper. Med. **58**:245, 1933.

Fifty-five persons were tested to determine the pneumococcidal promoting activity of their serum against pneumococci of types I and II. By repeated tests an attempt was made to study the constancy of the degree of their immunity over intervals of from two to six months. In this group were included nine persons with common colds and twelve with a severe influenza-like infection. Fifteen of the fifty-five persons tested showed a change in titer of their humoral immunity against either type I or II or both. Three of these showed an increase, and twelve a decrease. In most instances this reaction was a specific one in that the altered reaction toward one type was not associated with a similar change toward the other type of pneumococcus. Colds and influenza-like infections apparently exerted no effect on the titer of humoral immune substances.

AUTHORS' SUMMARY.

STREPTOLYSINS. B. E. HODGE and H. F. SWIFT, J. Exper. Med. **58**:277, 1933.

Certain properties of streptolysin in respect of hemolytic power and capacity for combining with antistreptolysins have been determined. The hemolytic strength may vary markedly, while under suitable conditions the combining power is constant. This stability of combining makes it possible to prepare a large amount of streptolysin, standardize it against serums of known antistreptolysin strength, and use it as a reagent over a considerable period for testing the antistreptolysin content of unknown serums. A modified technic for making these tests is described.

AUTHORS' SUMMARY.

VACCINATION OF RABBITS WITH PARTIALLY DEFATTED TUBERCLE BACILLI. K. C. SMITHBURN, J. Exper. Med. **58**:329, 1933.

A vaccine prepared from partially defatted bovine tubercle bacilli favorably influenced the survival time after inoculation with living virulent bovine tubercle bacilli. Accompanying this increased resistance was a sustained lymphocytosis in

the vaccinated animals. The vaccine induced a transitory anemia and leukopenia. A similar preparation of partially defatted human tubercle bacilli possessed the power to sensitize guinea-pigs to tuberculoprotein. AUTHOR'S SUMMARY.

THE ANTIGENIC COMPLEX OF THE MENINGOCOCCUS. G. RAKE and H. W. SCHERP, J. Exper. Med. **58**:341 and 361, 1933.

Three fractions have been isolated from autolysates of the meningococcus. Of these, one, the type-specific substance, has been described in detail. The same type-specific substance appears to be present in organisms of types I and III, but a substance differing at least serologically has been obtained from strains of type II.

Two group-specific substances, one a polysaccharide and the other a protein, have been isolated from the meningococcus. Their serologic properties are described. AUTHORS' SUMMARY.

MENINGOCOCCUS PRECIPITINOGENS IN THE CEREBROSPINAL FLUID. G. RAKE, J. Exper. Med. **58**:375, 1933.

Precipitin tests on the cerebrospinal fluid from cases of meningococcic meningitis with monovalent serums demonstrate the presence of type-specific precipitinogens of the meningococcus. Negative results are secured when the spinal fluid is obtained after the commencement of intrathecal serum treatment and also occasionally when the numbers of infecting organisms are very small. The reaction offers an easy and rapid method of ascertaining to which type of meningococcus a particular case of meningitis is due, and facilitates the immediate use of monovalent therapeutic antimeningococcus serum. Typing by means of the precipitin reaction can be confirmed by agglutination of the strain of organism responsible for the infection, if such a strain is isolated. Confirmation by means of agglutination has been possible in all the cases discussed in this report. Spinal fluids from patients with other diseases of the meninges and central nervous system fail to give any precipitin reaction with the monovalent serums. AUTHOR'S SUMMARY.

THE SPECIFICITY OF ALLERGY TO CERTAIN NEISSERIAE. C. P. MILLER and R. CASTLES, J. Exper. Med. **58**:435, 1933.

By means of the reaction to intracutaneous inoculation with bacterial suspensions in amounts of 0.1 cc., bacterial allergy was demonstrated in rabbits into which agar foci containing gonococci, meningococci, Micrococcus catarrhalis, or Bacterium lepisepticum had been implanted. The criterion of hypersensitiveness is the relative size and intensity of reaction evoked by an identical dose in "agar focus" and control rabbits. Rabbits sensitized to gonococci or meningococci usually reacted indistinguishably to either of these organisms, but were less allergic to M. catarrhalis. Similarly, animals sensitized to M. catarrhalis gave moderate but not maximal responses to gonococci and meningococci. Cross-reactions did not occur between Bact. lepisepticum and any of the three cocci. Animals sensitized to the four organisms mentioned reacted no more intensely than did controls to hemolytic streptococci, staphylococci and rough pneumococci. The hypersensitive state was found to begin early in the second week and to end usually by the fourth week, being at its height in most instances from the tenth to the twelfth day. The number of organisms contained in the agar focus determined the success of the sensitization only to the extent that very small and very large inoculations failed to produce the allergic state. In rabbits immunized by the intravenous injection of living organisms cutaneous reactions indistinguishable from those in controls developed. The "secondary rise" of Andrewes, Derick and Swift was rarely observed.

AUTHORS' SUMMARY.

THE INFLUENCE OF TESTICLE EXTRACT UPON THE EFFECT OF TOXINS, BACTERIA AND VIRUSES, AND ON THE SHWARTZMAN and ARTHUS PHENOMENA. F. DURAN-REYNALS, J. Exper. Med. **58**:451, 1933.

The lesions produced by the Shwartzman and Arthus phenomena, as well as those produced by bacterial toxin and foreign serums in the normal rabbit, are spread by testicular extract over a larger area than would otherwise be covered. With this spreading of the lesions there is a definite reduction in their intensity. Lesions produced by invasive strains of staphylococci in high dilutions or by non-invasive staphylococci at moderate dilutions are definitely lessened in severity or even suppressed by the spreading action of testicular extract. Lesions due to virus are consistently enhanced by the spreading factor, regardless of the dilution.

AUTHOR'S SUMMARY.

NEUTRALIZING ANTIBODIES IN ABORTIVE POLIOMYELITIS. J. D. TRASK and J. R. PAUL, J. Exper. Med. **58**:531, 1933.

The neutralizing antibody content for poliomyelitis virus has been tested with both a human and a passage strain of the virus in serial samples of serums from five mild cases of abortive poliomyelitis, and an increase in this antibody content has been demonstrated in samples of convalescent serum obtained within four weeks of the acute illness.

AUTHORS' CONCLUSION.

TYPE-SPECIFIC SERUM AGAINST HEMOPHILUS INFLUENZAE. M. PITTMAN, J. Exper. Med. **58**:683, 1933.

Most of the strains of Haemophilus influenzae that cause meningitis are of the same serologic type (b). A horse immunized with a strain of type b gave a highly type-specific serum with marked anti-infectious action in mice and rabbits. The evidence at hand indicates that this serum may have practical value in influenzal meningitis.

THE SOLUBLE SPECIFIC SUBSTANCE OF PNEUMOCOCCUS TYPE I. O. T. AVERY and W. F. GOEBEL, J. Exper. Med. **58**:731, 1933.

The soluble specific substance of Pneumococcus type I is now regarded, tentatively at least, as an acetyl polysaccharide. In this form it accounts adequately for all the serologic phenomena of type specificity of Pneumococcus type I.

AUTHORS' CONCLUSIONS.

TISSUE CULTURE STUDIES ON THE RELATION OF THE TUBERCULIN REACTION TO ANAPHYLAXIS AND THE ARTHUS PHENOMENON. J. D. ARONSON, J. Immunol. **25**:1, 1933.

The growth and migration of cells in explants from the spleen and bone marrow of tuberculous guinea-pigs are inhibited by the addition of tuberculin; those explanted from nontuberculous guinea-pigs sensitized by a single injection of horse serum are not inhibited by horse serum. Migration and growth in similar explants from tuberculous guinea-pigs sensitized to horse serum are not inhibited by the addition of horse serum; they are, on the other hand, inhibited by tuberculin. When the Arthus phenomenon was elicited by injections of horse serum into normal and tuberculous guinea-pigs the tissue cultures were unaffected by the addition of the serum. These experiments on tissue cultures suggest that the mechanism underlying the tuberculin reaction is different from the mechanisms of anaphylaxis and the Arthus phenomenon.

AUTHOR'S SUMMARY.

THE URTICARIAL SKIN REACTIONS IN GUINEA-PIGS. L. S. PILCHER, JR., J. Immunol. **25**:11, 1933.

Cutaneous reactions typical of urticaria and exactly resembling in character and time sequence those described in man by Lewis and Grant were produced in

guinea-pigs by light skin puncture through a drop of 1:100 solution of histamine. The vascular changes preceding and accompanying the urticarial reaction could be accurately observed by looking through the ear of the guinea-pig while the reaction was in progress. "Immediate" anaphylactic cutaneous reactions to antigenic horse serum were produced in sensitized guinea-pigs by light puncture of the skin through a drop of undiluted horse serum. These reactions were typically urticarial, resembling the wheals produced by histamine but having a more gradual and chronic sequence of development. No general anaphylactic reactions of any kind accompanied any of the cutaneous reactions. The anaphylactic sensitivity of all the animals tested was checked by an intracardiac injection of 2 cc. of normal horse serum at the end of the experiment. There appeared to be a fairly definite relation between the presence of general anaphylactic sensitivity and the production or nonproduction of the typical anaphylactic sensitivity and the degree of production of the cutaneous reaction caused by histamine. AUTHOR'S SUMMARY.

IMMUNIZATION OF RABBITS WITH HEAT-KILLED TUBERCLE BACILLI. J. HUGHES, J. Immunol. **25**:103, 1933.

The serum of rabbits vaccinated by repeated injections of heat-killed tubercle bacilli shows a progressive increase in its ability to promote phagocytosis of living tubercle bacilli by polymorphonuclear and mononuclear cells. The close parallel in the bacteriotropic action of the serum on polymorphonuclear and on mononuclear leukocytes indicates that the same antibody is concerned in the phagocytosis of tubercle bacilli by the two types of cell. The earliest manifestation of bacteriotropic action precedes the onset of sensitization, indicated by the cutaneous reaction to an injection of dead tubercle bacilli. Infection with living tubercle bacilli has caused an earlier appearance of bacteriotropic substance than repeated injections of the dead organism, but the titer attained is no higher. AUTHOR'S SUMMARY.

LOCAL ORGAN HYPERSENSITIVENESS. B. C. SEEGAL, S. SEEGAL and D. KHORAZO, J. Immunol. **25**:207 and 221, 1933.

When 0.15 cc. of undiluted egg white is injected into the anterior chamber of the rabbit's eye, traces may be found for as long as eight days. The egg white can never be demonstrated in the serum or the fluid in the anterior chamber of the other eye. The injection of 0.15 cc. of undiluted egg white into the anterior chamber is followed by the appearance of precipitins against egg white in the serum. The precipitins reach a titer of 1:20,000 or more in about nine days. Precipitins may also be found in the aqueous humor of the eye into which egg white has been injected, though they do not always appear there. In only one animal did they reach a titer as great as that of the serum precipitins. Precipitins never appear in the fluid in the anterior chamber before they appear in the serum. Precipitins are never found in the fluid in the anterior chamber of the other eye. When 0.2 cc. of egg white is injected into rabbits in a single dose subcutaneously, intravenously or intracutaneously no precipitins against this antigen appear in the serum. When the same amount of egg white is diluted and injected in four divided doses subcutaneously or intravenously the serum contains precipitins against egg white to the same titer as that obtained by injecting 0.2 cc. of the antigen into the anterior chamber of the eye. The rabbit's eye was passively sensitized by the injection of rabbit anti-egg-white-serum into the anterior chamber only once in nine attempts. If animals which have been locally sensitized in the eye are allowed to rest until no antigen remains in the fluid in the anterior chamber and are then given an injection of a "shocking" dose of antigen intravenously, the eye becomes inflamed. During the period of inflammation the fluid in the anterior chamber of the sensitive eye may contain traces of the antigen. The appearance of antigen in the fluid in the anterior chamber of a reacting eye may furnish an explanation for the continuation of the hypersensitive stage in this organ, since fresh antigen is available for the stimulation of further sensitivity.

In rabbits whose right eye was inflamed by the introduction of glycerin into the anterior chamber, repeated intravenous injections of egg white resulted in a specific local sensitization of the eye to egg white in twelve of twenty-one animals tested. In control rabbits receiving intravenous injections of egg white alone and in other animals whose right eye was injured with glycerin alone the ocular reaction did not develop when the test dose of egg white was injected intravenously. Repeated injections of egg white intravenously in normal animals may bring about a degree of general reactivity causing later injections of egg white to produce bilateral inflammation of the eyes.

AUTHORS' SUMMARY.

NONSPECIFIC PRECIPITINS FOR PNEUMOCOCCIC FRACTION C IN ACUTE INFECTIONS. R. ASH, J. Infect. Dis. **53**:89, 1933.

Precipitins against the pneumococcic fraction C described by Tillett and his associates appear early in the course of acute infectious disease and disappear shortly after the cessation of the infection. These precipitins are not restricted to pneumococcic infection but may occur in illnesses due to gram-negative as well as to gram-positive organisms. These precipitins have not been noted in syphilitic infection and appear in only small amounts, if at all, in tuberculous disease. In many instances there is a relationship between fever, an increased rate of sedimentation and this phenomenon of precipitation, but the relationship is not constant. The phenomenon is not one of maturation, related to age or to previous infection, since it may be observed in early infancy.

AUTHOR'S SUMMARY.

AGGLUTINATION TESTS IN THE DIAGNOSIS OF INFECTIOUS ABORTION IN CATTLE. C. R. DONHAM and C. P. FITCH, J. Infect. Dis. **53**:98, 1933.

The sensitivity of Bacterium abortus agglutination antigen for either the test tube or the rapid test method is increased for most agglutinating serums by the addition of either acacia or gelatin to the antigen. It is not uncommon to encounter agglutinating serums having identical test tube titers that do not respond in the same manner when tested with various kinds of rapid test antigen. The rapid and the test tube method should be standardized each by itself and not one on another. The influence of varying concentrations of electrolytes (as such) in the rapid test method of testing appears to be similar, if not identical, with that in the test tube method. At present, the tests cannot be carried out in the complete absence of electrolytes. Heating rapid test Bact. abortus antigen does not exert any significant influence on its sensitivity. The coagulum formed on the surface of a boiled rapid test suspension of antigen has antigenic properties indistinguishable from those of the balance of the boiled antigen. There is no evidence to indicate that the removal of the coagulum increases the sensitivity of the antigen. Titers can be varied by changing the amounts of the antigen. The size of the drops delivered with dropper pipets as they have been supplied with commercial rapid test antigens varies more than the limits within which variation in the amounts of antigen does not yield consistent differences in the titers. A mathematical analysis of the titers obtained in rapid tests of bovine serums by different observers and with different preparations of antigen shows significant variations in the results. Atypical clumping of rapid test antigen may occur. The activity of specific agglutinin for Bact. abortus is not appreciably influenced by evaporating the agglutinating serum to dryness.

AUTHORS' SUMMARY.

PRECIPITATED DIPHTHERIA TOXOID. L. C. HAVENS and D. M. WELLS, J. Infect. Dis. **53**:138, 1933.

The precipitation and purification of diphtheria toxoid by potassium-aluminum sulphate are described. Complete precipitation results from the addition of from 1 to 2.5 per cent of alum. There is little or no loss of specific antigen, while nitrogen determinations show that the protein content is reduced to from 13 to 20 per cent of the original amount. The antigenic activity of the precipitate is superior to that

of ordinary toxoid. Subcutaneous injection of 0.1 cc. (1 unit) into guinea-pigs protects them against a subsequent injection of at least 5 minimum lethal doses of toxin, while 5 units of the precipitate has protected guinea-pigs against 450 minimum lethal doses. A single injection of from 5 to 10 units given to children has resulted in negative reactions to the Schick test in 96 per cent of these children. The superior antigenic character of the precipitated toxoid is probably due to its slow absorption with the resultant prolonged immunizing action.

AUTHOR'S SUMMARY.

IMMUNIZATION OF SHEEP TO THE VIRUS OF POLIOMYELITIS. B. F. HOWITT, J. Infect. Dis. **53**:145, 1933.

It has been demonstrated that antiviral substances may be produced by repeated inoculations of poliomyelitic virus into a refractory animal such as the sheep. The immunization was accomplished in two animals within five months, not only by giving centrifugated suspensions of virus, but by inoculating the washed acetone precipitate of such a suspension. Serums of comparable potency were produced by each method. Serums obtained from these animals neutralized the 5 per cent monkey passage strain of virus in final dilutions of 1:200, 1:400 and, in the case of sheep, 404, even 1:800, while that from sheep 117, which was killed after three years of immunization, gave a titer of from 1:100 to 1:200. The latter serum was found to retain its potency for at least thirteen months. It also showed as high a titer as the serum from a patient who had recovered from poliomyelitis, while two other human serums failed to give protection in the same dilutions as the sheep serums. Human serums stored from nine to eleven months in the icebox were found to retain the same neutralizing power for the old virus as that formerly observed. Identical results were also noticed with serums obtained one year after an earlier bleeding. Comparative neutralization tests with both immune sheep serum and human convalescent serum, respectively, against an old and a more recently isolated strain of poliomyelitic virus (New York, 1931) gave evidence of a certain modification of the old virus after repeated passage through monkeys. If the laboratory virus can be definitely altered by prolonged passage through a new host, it is advisable to employ a recently isolated strain both for work on immunization and for testing the antiviral power of immune serums.

AUTHOR'S SUMMARY.

RELATION OF ALLERGY TO GENERAL RESISTANCE IN STREPTOCOCCIC INFECTION. B. J. CLAWSON, J. Infect. Dis. **53**:157, 1933.

Resistance to streptococcic infection can be developed artificially without producing a measurable amount of hypersensitiveness (allergy). The state of streptococcic allergy bears no necessary relation to general resistance. Allergy as related to general resistance to streptococci seems to be a useless and at times a harmful concomitant phenomenon.

AUTHOR'S SUMMARY.

HETEROPHILIC ANTIBODIES IN SERUM DISEASE. I. DAVIDSOHN, J. Infect. Dis. **53**:219, 1933.

The difference in the development of the heterophilic antisheep agglutinin and hemolysin, as contrasted with the nonheterophilic antirabbit antibodies, points to the Forssman antigen in the injected horse serum as the responsible antigenic factor.

AUTHOR'S SUMMARY.

NEUTRALIZATION OF POLIOMYELITIS VIRUS. N. P. HUDSON and W. LITTERER, J. Infect. Dis. **53**:304, 1933.

The serums of twenty-five normal adult white residents of Nashville, Tenn., were tested for ability to neutralize the virus of poliomyelitis. Twenty-one specimens were virucidal when examined without dilution, and sixteen of these neutral-

ized the virus when tested again in a further dilution of 1:5. An analysis of the age of the donors in relation to the results showed that those of the upper age group (30 to 44 years) had a higher proportion of neutralizing serums and that more specimens were virucidal in the arbitrarily chosen dilution of 1:5, than those of the lower age group (17 to 29 years). Cases of poliomyelitis have occurred in Nashville and in other parts of Tennessee for many years, without, however, causing the appearance of epidemics. Most of the cases occurred in areas of denser population, but even sparsely settled counties reported cases of the disease more or less frequently. Our experimental results are consistent with the epidemiologic features of the disease in Southern states. Before we conclude, however, whether the neutralizing property demonstrated is a specific response to exposure to the virus of poliomyelitis or whether it is a manifestation of serologic ripening with maturation of the person, further observations and experimentation must be made. The high proportion of persons examined whose serum neutralized virus gives a basis for experimentation in the use of such serum in poliomyelitis.

AUTHORS' SUMMARY.

PRECIPITIN PRODUCTION IN RABBITS FOLLOWING INTRAMUSCULAR INJECTION OF ANTIGEN ADSORBED BY ALUMINUM HYDROXIDE. L. HEKTOEN and W. H. WELKER, J. Infect. Dis. **53**:309, 1933.

In rabbits a single intramuscular injection of aluminum hydroxide carrying a measured quantity of antigen may induce the continuous formation of precipitin for many months. The aluminum hydroxide appears to be gradually replaced by connective tissue. Antigens adsorbed on aluminum hydroxide do not separate on standing and retain their precipitinogenic properties for at least twelve months and probably much longer. Aluminum hydroxide may carry at least ten distinct, specific antigens at the same time, and the rabbit may respond to a single intramuscular injection with the specific production of precipitin for each of the ten antigens.

AUTHORS' SUMMARY.

SHWARTZMAN PHENOMENON. H. M. KLEIN, J. Infect. Dis. **53**:312, 1933.

Evidence is presented that in patients recovering from systemic gonococcic infections and from typhoid fever specific antitoxins developed spontaneously, as demonstrated by the Shwartzman phenomenon. It appeared highly suggestive that in these patients recovery was related to the formation of antitoxin. The serum of certain patients with previous meningococcic infections and of certain controls was shown to possess meningococcic antitoxin. This was group specific. The capacity of antigonococcic serum to neutralize meningococcus-reacting factors and of antimeningococcic serum to neutralize gonococcus-reacting factors is a further evidence of the biologic relationship between the gonococcus and the meningococcus. These investigations are being extended to the other diseases caused by bacteria possessing toxins potent in eliciting the Shwartzman phenomenon. The aim will be to study whether spontaneous formation of antitoxin takes place. If further studies are fruitful, attempts should be made to confer immunity against this entire group of diseases, actively by prophylactic injections of toxoid and passively by the administration of immune serums to actively ill patients.

AUTHOR'S SUMMARY.

TETANUS TOXOID IN PROPHYLAXIS AGAINST TETANUS. D. H. BERGY and S. ETRIS, J. Infect. Dis. **53**:331, 1933.

Experiments with tetanus toxoid on guinea-pigs showed that three doses of 1 cc. each bring about a high degree of protection. From the results obtained in guinea-pigs, it is believed that man may also be protected against tetanus by the administration of several doses of toxoid. This method of protection obviates the hypersensitization against horse serum that may occur from passive immunization with tetanus antitoxin.

AUTHORS' SUMMARY.

THE PURIFICATION OF DIPHTHERIA TOXOID. G. F. LEONARD and A. HOLM, J. Infect. Dis. **53**:376, 1933.

A method for the purification of toxoid on a large scale should meet the following requirements: easy manipulation, satisfactory yield, elimination of more than 50 per cent of the nonspecific protein, flocculation, sterilization by the Berkefeld filter, stability for at least one year, and a higher antigenic efficiency than the average crude toxoid. None of the methods tested has met all these requirements. Precipitation by ammonium sulphate with subsequent dialysis and precipitation by acetone and by alum gave the highest yields as measured by flocculation with antitoxin. The immunizing value of toxoids precipitated by alum was found to be far superior to that of the crude toxoids. AUTHORS' SUMMARY.

Tumors

HISTOLOGIC GRADING OF CARCINOMA OF THE BREAST. C. D. HAAGENSEN, Am. J. Cancer **19**:285, 1933.

In a series of 164 cases of carcinoma of the breast, which was exceptionally advantageous for a study of the relationship of histologic structure to prognosis because of the remarkably complete follow-up data and because of the superior quality and the large number of the histologic sections, a careful analysis has been made as to the prognostic significance of fifteen different histologic characteristics. Six of these characteristics have been found to have a probable relationship to the end-result of treatment. These significant characteristics are, in fact, similar to those which Hansemann originally proposed for the determination of the grade of anaplasia. The factors of fibrosis and lymphocytic infiltration, recently stressed in tumor grading, have been found to be without prognostic import. On the basis of these six significant histologic characteristics it would appear that carcinomas of the breast can be classified into three grades of malignancy, in which increasing grade of anaplasia parallels increasing grade of malignancy as evidenced by the tendency of the tumor to metastasize and kill the patient at an early date. It should be remembered that a prognosis based on this type of histologic evidence cannot claim mathematical accuracy. It should be regarded as an approximation and a rough one at that. Malignancy is a biologic phenomenon and does not lend itself to exact measurement in mathematical terms. Moreover, the extremes, that is, grades 1 and 3, should be given more weight than grade 2, the less definite middle class into which a great proportion of carcinomas of the breast fall. Knowledge gained from histologic grading should not be regarded as competing with clinical data bearing on prognosis, to which it is, of course, subordinate in importance. Histologic grading should rather be considered as a new and additional, a modest yet valuable increment to knowledge of the disease.

AUTHOR'S SUMMARY.

HISTOLOGICAL FACTORS IN THE PROGNOSIS OF MAMMARY CANCER. W. A. EVANS, JR., Am. J. Cancer **19**:328, 1933.

An analysis of some microscopic characteristics in regard to prognosis has been made in seventy-five operable cases of carcinoma of the breast treated by radical operation and short wavelength radiation. In considering the series as a whole, anaplasia (lack of differentiation) with respect to tubule formation, characteristics of the cytoplasm and irregularities of the cells indicates a shortened postoperative duration of life. The difference, however, is so slight that in the individual case anaplasia is of no practical importance in determining the outcome. The relative amount of fibrous tissue stroma is of no significance. A high degree of lymphocytic infiltration appears to be unfavorable. The addition of radiation therapy to surgical treatment does not appear to alter the factors on which a prognosis may be based.

AUTHOR'S CONCLUSIONS.

HISTOGENESIS OF EWING'S SARCOMA OF BONE. P. J. MELNICK, Am. J. Cancer **19**:353, 1933.

A consideration of the histogenesis of Ewing's sarcoma of bone leads to the following conclusions: It is not an endothelioma, because tumors derived from endothelium can only be identified by their possession of unmistakable vasoformative properties. It is not a reticulo-endothelial sarcoma, because it possesses few of the morphologic and none of the physiologic characteristics of the cells of the reticulo-endothelial system. It is not a form of myeloma, because the blood elements that are apparently a feature of some cases are probably part of the reactive process of periosteal new formation of bone and bone marrow in the periphery that is characteristic of this tumor. It is an undifferentiated round cell sarcoma. It probably originates from the undifferentiated embryonic mesenchymal cells in the connective tissue about the blood vessels in the haversian canals.

AUTHOR'S SUMMARY.

POLYMORPHOUS SARCOMA OF THE UTERUS. R. J. NEEDLES, Am. J. Cancer **19**:364, 1933.

Sarcoma of the uterus presents a varied cell picture and a certain degree of polymorphism. There is, however, a small group of tumors of the uterus with a cell picture so varied that they deserve to be termed "polymorphous sarcomas." Endotheliomas and giant cell tumors of the uterus show a similarity to certain cell groups found in polymorphous sarcoma. More thorough examination of different portions of some of these tumors might result in their being transferred to the polymorphous group. Three cases are reviewed which seem undoubtedly members of this group. A new case is reported, which makes a total of four cases to date.

FROM AUTHOR'S CONCLUSIONS.

THE CALCIUM, POTASSIUM, AND INORGANIC PHOSPHATE CONTENT OF THE BLOOD IN CANCER. H. JACKSON, JR., and F. H. L. TAYLOR, Am. J. Cancer **19**:379, 1933.

In thirty-one patients with malignant disease the blood calcium was within normal limits or above in approximately 50 per cent of the cases. The evidence indicates that the hypocalcemia existing in some cases of cancer is due to disturbed nutrition and not to cancer per se. An analysis of the thirty-one cases is presented with respect to the duration and localization of the tumor, the loss of body weight, the involvement of the bones and the gastro-intestinal tract and the age of the patient in relationship to the blood calcium. There were no changes in the level of the potassium or of the inorganic phosphate of the serum. Data are presented on the influence of roentgen therapy on some of the more important inorganic blood constituents. Intensive irradiation appears to be without effect on these substances in cases of cancer.

AUTHORS' SUMMARY.

TAR CANCER IN MICE ON DIETS SUPPLEMENTED WITH FRESH LIVER. A. F. WATSON, Am. J. Cancer **19**:389, 1933.

There is an increased carcinogenic response in tar-treated mice when the diet on which they are maintained is supplemented with fresh liver. The increased response is shown by the earlier appearance of the benign warts and by the larger numbers of animals that have warts and epitheliomas. On the other hand, the average interval of time between the first treatment with tar and the development of malignant growth is not reduced. If the administration of liver is discontinued after the appearance of the warts, there is no difference in the rate of development of malignancy. The results indicate that it is possible to modify the susceptibility of a tissue to the development of malignancy in response to the action of a carcinogenic agent. Under the experimental conditions adopted, this modification influences the rate of appearance and the numbers of warts; it also affects the

number of malignant tumors, but it does not accelerate the onset of malignancy. This suggests that the development of benign hyperplasia is conditioned, partly at any rate, by different factors. AUTHOR'S SUMMARY.

INFECTIOUS PAPILLOMATOSIS OF RABBITS. R. E. SHOPE, J. Exper. Med. **58**:607, 1933.

A papilloma has been observed in the wild cottontail rabbit and has been found to be transmissible to both the wild and the domestic rabbit. The clinical and pathologic pictures of the condition have been described. It has been found that the causative agent is readily filtrable through Berkefeld but not regularly through Seitz filters, that it stores well in glycerol, that it is still active after heating to 67 C. for thirty minutes, but not after heating to 70 C., and that it exhibits a marked tropism for cutaneous epithelium. The activities and properties of the papilloma-producing agent warrant its classification as a filtrable virus. Rabbits carrying experimentally produced papillomas are partially or completely immune to reinfection and, furthermore, their serums partially or completely neutralize the causative virus. The disease is transmissible to domestic rabbits, producing in this species papillomas identical in appearance with those found in wild rabbits. However, the condition is not transmissible in series through domestic rabbits. The possible significance of this observation has been discussed. The virus of infectious papillomatosis is not related immunologically either to the virus of infectious fibroma or to that of infectious myxoma of rabbits. AUTHOR'S SUMMARY.

MITOGENIC RADIATION BY CERVICAL CANCER. J. KLENITZKY, Ztschr. f. Krebsforsch. **39**:60, 1933.

Klenitzky describes an apparatus by which he was successful in detecting mitogenic radiation by cervical cancers in situ. The phenomenon was constantly present, but it occurred as well in certain noncancerous conditions—notably erosions—so that it cannot be used as a differential diagnostic measure. Nor is absence of the radiation in cancerous blood of diagnostic value, since this, too, may occur in other diseases; also, with squamous cell cancers, the radiation in the blood may persist. In a mouse with a transplanted adenocarcinoma, radiation in the blood returned after successful extirpation of the tumor and persisted until the death of the animal. H. E. EGGERS.

CILIATED EPITHELIAL CYST OF THE LIVER. W. DULLIN, Ztschr. f. Krebsforsch. **39**:80, 1933.

In connection with this brief report on a case of ciliated epithelial cyst of the liver, Dullin states that it is the sixteenth case of the sort to be reported.

H. E. EGGERS.

SEASONABLE FLUCTUATIONS IN THE MORTALITY FROM CANCER. P. GEREB, Ztschr. f. Krebsforsch. **39**:104, 1933.

Known seasonal fluctuations in death rates are caused ordinarily by a complex of factors frequently defying definite evaluation. The incidence of certain infections and that of diseases due more or less directly to vitamin deficiencies reach their apex in the winter and spring; respiratory diseases and infantile spasmophilia are most frequent in the spring; intestinal infections, especially those of children, in summer; typhoid fever, in late summer and fall. In general, however, the maximum total death rate occurs in the first half of the year. Cancer is an interesting exception to this, as the mortality from it reaches the highest point in the last half of the year, standing in this respect in definite contrast to that from tuberculosis, with which the reverse is true. A similar periodic variation is shown in the rate of growth of transplanted tumors, and Gereb calls attention to the fact that this period of apparent greatest growth of tumors occurs at the time of an ample sufficiency of vitamins in the diet. H. E. EGGERS.

MIXED TUMOR OF THE BREAST IN DOGS. K. NIEBERLE, Ztschr. f. Krebsforsch. **39**:113, 1933.

The mixed tumor of the breast appears to be the commonest one at that site in the dog just as in the human being it is the commonest one in the parotid gland. In the course of one year Nieberle saw fifty such tumors, while in the same period he saw only seven carcinomas and one adenofibroma of that organ. Almost without exception they were perfectly encapsulated and definitely benign. Like similar tumors in man, they sometimes showed wide variation in the morphologic elements. Glandular epithelium was quite constant, in the form of tubules or in that of simple or papillary cysts. Stratified squamous epithelium was more rare. Mucoid connective tissue was fairly constant, and cartilage was frequent; occasionally they contained bone; another element seen with some frequency was a nest of reticular cells. In regard to the origin of such tumors, Nieberle dismisses absolutely the endothelial theory of Volkmann, as well as that of purely epithelial derivation. He regards them as resulting primarily from aberrant embryologic development, with the diversity of stroma being due to the effect, on undifferentiated mesenchyme, of the adjacent epithelial structures.

H. E. EGGERS.

NERVES IN TUMORS. M. N. MEISSEL, Ztschr. f. Krebsforsch. **39**:128, 1933.

Meissel used in this study of the nerve supply in malignant tumors those developing in tarred mice at sites remote from the areas of tarring. Both precancerous papillomas and squamous cell carcinomas were studied. In both there were abundant nerve fibers, reaching, in the former, to the keratinized cells, and originating in the nerve supply of the hair follicles; in the malignant tumors they appeared for the most part to be newly grown, and this growth could be traced back to nerve cords in the underlying connective tissue. Where nerve cords were compressed by the growing tumor they showed marked degeneration and active regeneration, similar to that seen after experimental trauma. Such regenerating and proliferating nerves penetrated through cancerous tissue, even reaching the epithelial pearls, and at times, in the form of fine filaments, establishing close contact with cancer cells. Some of them were of the morphologic type of the normal intra-epithelial nerves. Consequently, in these tumors there were remnants of nerves previously present, as well as such as were newly introduced through the processes of proliferation and regeneration.

H. E. EGGERS.

CANCER OF THE ANTRUM AND METAPLASIA. W. SCHÜTZ, Ztschr. f. Krebsforsch. **39**:152, 1933.

In a study of the mucosa of the antrum in fifty cases, Schütz could detect with certainty metaplasia in four, cylindric epithelium being altered to that of squamous cell or undifferentiated (basal cell) type. Morphologically, this appeared to be metaplasia of the type which Teutschlaender designated as prosoplastic. Metaplasia by dedifferentiation, either direct or indirect, did not appear to occur. The change was apparently accomplished by the basal cells. Schütz regards it as a precancerous process which in suitable subjects develops into malignant neoplastic growth.

H. E. EGGERS.

A PRIMARY CARCINOMA OF MECKEL'S DIVERTICULUM. K. FRANKE, Ztschr. f. Krebsforsch. **39**:206, 1933.

A man, 54 years of age, with the symptoms of acute ileus, was found to have, about 1.25 mm. above the ileocecal valve, a superficially ulcerated tumor from which there escaped slimy mucoid material enough to fill the peritoneal cavity. Its diverticular character was evident grossly; histologically, its structure was that of a colloid cancer; there were, however, no metastases, and the course since its removal has been uneventful.

H. E. EGGERS.

Society Transactions

PATHOLOGICAL SOCIETY OF EASTERN NEW YORK

ARTHUR W. WRIGHT, *Secretary*

Regular Meeting, June 15, 1933

R. J. LEBOWICH, *Presiding*

FIBROMYOMA OF THE ASCENDING COLON. R. J. LEBOWICH.

At autopsy there was found in the ascending colon a solitary, roughly circular growth measuring 9 by 7.5 by 7 cm. This growth was freely movable, sharply circumscribed, completely encapsulated and covered over its superior surface by the markedly atrophied mucosa of the colon. It partly obstructed the lumen of the intestine. On section, the characteristic structure of a fibromyoma was revealed, free from degenerative or malignant changes.

Microscopic sections of the entire growth, stained with hematoxylin and erythrosin and with van Gieson's stain, showed equal amounts of fibrous tissue, focally hyalinized, and interlacing bundles of smooth muscle cells, uniform in size, shape and staining qualities.

PRIMARY CARCINOMA OF THE LUNG. G. H. KLINCK, JR., and V. C. JACOBSEN.

CASE 1.—A white man, 59 years of age, was admitted to the psychiatric service because of moodiness and morbid ideas. Six weeks previously hoarseness had developed, followed by pain in the chest and abdomen. He gradually became stuporous, began to have difficulty in swallowing and died two weeks later.

At autopsy, the left lung weighed 450 Gm. There was a mass of lymph nodes, 8 cm. in diameter, at the hilus. These showed neoplastic invasion. In the bronchus there was a nodular tumor which greatly narrowed the lumen and spread into the adjacent pulmonary tissue. No other mass was found. The nodular tumor was found to be continuous with a neoplastic mass, 2.5 by 1 by 1 cm., in the pulmonary substance. The right lung was not involved. The liver, kidneys and suprarenal glands showed extensive metastases.

Microscopically, the tumor in the left bronchus was a carcinoma infiltrating beneath and eroding through the bronchial mucosa. There was a circumscribed infiltration of the pulmonary substance in this region. The tumor was composed of oat-shaped epithelial cells, which in places maintained a more or less parallel arrangement. There were numerous mitoses and many large areas of necrosis. Secondary growths which were identical histologically with the parent tumor were found in the kidneys, suprarenal glands and brain.

CASE 2.—A white man, 78 years of age, noticed a nodule in the lower portion of the right side of his neck. Biopsy showed a spindle cell carcinoma. The primary tumor could not be found. He became comatose and died three days later.

At necropsy, the left lung weighed 810 Gm. and contained a large, firm tumor in the superior half of the upper lobe. The bronchus showed an elevated, firm, white, nodular growth 2 or 3 cm. from the bifurcation of the trachea. From this point the growth spread out in a rather fan-shaped manner over an area 4 by 6 cm. The lower lobe of the left lung was free from nodules. The right lung contained numerous small, hard nodules from 1 to 3 cm. in diameter. The liver, both kidneys, the left suprarenal gland and the mesenteric, retroperitoneal and mediastinal lymph nodes contained metastases. In the bladder numerous diverticula

were present, the largest measuring about 3 cm. in diameter. In this large pouch was found a firm, slightly fungating mass 3 cm. in diameter, occupying almost the entire thickness of the wall. No calculi were present.

Microscopic examination of the left lung showed a primary medullary carcinoma arising in the left bronchus. It had invaded widely, and groups of tumor cells were found in many blood and lymph vessels. The cells in places suggested origin either from glandular or from ciliated epithelium. Necrosis was present in the larger masses and mitoses were frequent. The hilar lymph nodes were heavily infiltrated with tumor. Metastases were present in the liver, suprarenal glands, prostate gland and vertebrae and in a diverticulum in the bladder.

The object in presenting these cases is twofold: It is first to draw attention to the fact that, in the state of New York at least, the incidence of cancer of the lung is increasing and, second, to demonstrate two well recognized types of primary bronchial carcinoma, the type in which small oat-shaped cells predominate and the type in which columnar or spindle-shaped cells are characteristic and which arises definitely in a glandular or a ciliated columnar cell. An unusual feature in the latter case was the metastasis to the diverticulum in the bladder, an origin in the diverticulum being ruled out. The tendency of pulmonary cancer to metastasize to the brain is worthy of emphasis.

Coronary Occlusion, Thrombosis in the Left Ventricle, Iliac Embolism and Gangrene of the Lower Extremities. J. J. Clemmer.

A white man, aged 57, while working as a night watchman, was seized with severe epigastric pain, followed by prostration. Five days later he complained of pain in his right leg and two days after that clinical signs of gangrene were observed in the right foot. The gangrene progressed to the leg and in a few days the left lower extremity became similarly involved. The gangrene of both feet and legs progressed and death occurred, hastened by terminal pneumonia, six weeks after the onset of the symptoms.

Necropsy revealed an enlarged heart, marked coronary sclerosis and recent occlusion of the descending branch of the left coronary artery. The myocardium in this region was partially replaced by young, vascular, fibroblastic tissue. Portions of the remaining myocardium showed retrograde changes. Mural or valvular thrombi were not present.

The aorta was sclerotic. A laminated fibrinous mass protruded from the right iliac artery and impinged on the opening of the left. Both legs and feet were gangrenous, the right more so than the left. Several relatively recent infarcts were found in the spleen. A single hemorrhagic infarct was present in the right kidney. There was terminal acute bronchopneumonia.

It is believed that the acute onset was due to the coronary occlusion. Soon a mural thrombus formed in the left ventricle. As the myocardium partially recovered it forced the thrombus into the systemic circulation. Small infarcts of the spleen and kidney resulted, but the main mass lodged in the right iliac artery. This protruding embolic mass grew by accretion until it produced obstruction of the left iliac artery. Gangrene of the lower extremities developed as a result of the impaired circulation.

Osteitis Fibrosa Associated with Parathyroid Adenoma. Ellis Kellert.

A man, 37 years of age, had symptoms of urinary disturbance for ten years. He frequently passed minute calculi and many pus cells in the urine. More recently there were loss of weight and signs of renal insufficiency. Roentgenograms of the kidneys did not reveal calculi or enlargement of the organs. Owing to pain in the bones, these were roentgenographed and a generalized osteitis fibrosa was observed. The neck appeared normal on inspection and palpation. Secondary anemia was present, and there was definite retention of nonprotein nitrogen. The calcium in 100 cc. of blood amounted to 15 mg. After a period of epigastric distress and vomiting, death took place in coma.

Necropsy was limited to examination of the neck and kidneys. There was no tumor of the stomach, intestine or suprarenal glands. The right kidney was one-third larger than the left. Each kidney contained abundant renal substance, which was markedly congested and studded throughout with numerous small and large calcific particles. In the cortices were many small cysts filled with yellowish fluid. The pelves contained small calculi, and their mucous surfaces were covered with puriform material. Microscopic examination showed many sclerosed glomeruli, foci of lymphocytic infiltration, castlike bodies in the tubules, marked fibrosis and calcification of the pyramids. Deposits of calcium were observed in the interstitial tissue and within the remains of tubules.

The thyroid gland appeared normal. Situated on the posterior surface of the lower pole of the right lobe was a yellowish, globular, firm, encapsulated nodule measuring 3.5 by 2.5 by 2.5 cm. The capsule was thick, fibrous, and partly calcified

Photograph of thyroid gland showing large parathyroid adenoma on posterior surface. Note enlarged parathyroid body just above the adenoma.

and had no direct connection with the thyroid substance. When the nodule was sectioned, the cut surface appeared pale brown, soft and friable, and there was a recent hemorrhage in the center. The parenchyma tended to split on handling. Two other parathyroid glands were identified, and these were distinctly enlarged. Microscopic examination of the tumor showed abundant but normal-appearing parathyroid gland tissue. The cells were sharply defined. Many of the nuclei were pyknotic. No mitoses were observed.

CARCINOSARCOMA OF THE BREAST. J. SCHLEIFSTEIN.

Tumors of the breast containing carcinoma as well as sarcoma are rare. The specimen now described appears to contain both carcinoma and sarcoma.

An unmarried woman, past middle age, complained of a lump of one year's duration in the lower part of the right breast which a month previously began to grow rapidly and became painful. Six months previously she thought that it was

becoming smaller and hoped that it would entirely disappear. The breast was removed under local anesthesia.

The specimen consisted of approximately the whole right breast, measured about 8 by 6 by 6 cm. and was covered with skin. A diffuse tumor with localized nodulations was felt. On section, most of the breast appeared to be invaded by new growth. Areas of hemorrhage and necrosis could be seen, as well as one large cavity about the size of a plum, filled with débris and necrotic material.

Sections from one part of the breast showed typical alveolar carcinoma with scanty stroma. However, those taken from the advancing edge of the tumor presented an entirely different picture: A diffuse sarcomatous growth consisting of large spindle cells with hyperchromatic nuclei containing numerous mitotic figures, as well as giant cells with bizarre mitoses and extremely large nuclei. Well formed carcinomatous alveoli seemed to be embedded in the sarcomatous stroma. In some areas, particularly where the sarcoma grew, hemorrhage and necrosis were seen. Sections stained with Mallory's phosphotungstic acid hematoxylin showed what appeared to be fibrils. It is unfortunate that the lymph nodes of the axillary region were not submitted for examination.

FIBRO-ADENOMA OF THE BREAST CONTAINING CARCINOMA AND CARTILAGE. J. SCHLEIFSTEIN.

Cheatle, in his vast experience with tumors of the breast, has seen only two neoplasms of this organ containing cartilage. The occurrence of this type of tumor in man appears to be unusual, although it is frequent in the dog. A case that I observed presents features of interest to both the clinician and the pathologist.

A married woman, aged 57, complained of a lump of three months' duration in the left breast. There was no pain or tenderness. The nipple was not retracted or deformed. A tumor about the size of a peach, firm and circumscribed, was felt. No glands were palpable in the axilla. At operation what appeared to be an encapsulated fibro-adenoma was easily enucleated.

A portion of the tumor, about 4 by 3 by 3 cm., was received. The tissue was found to be rather firm, grayish white and fibrous with occasional chalklike specks embedded in it. Toward the center there was a minute, grayish-white, glistening nodule.

The microscopic examination showed an anaplastic, malignant growth, having the characteristics of an epithelial tumor, invading and infiltrating the fibro-adenoma. Hyperchromatic nuclei, numerous mitotic figures and some giant cells were found. Toward the center of the section a small nodule of cartilage was observed. Whether the carcinoma originated elsewhere in the breast and invaded the fibro-adenoma or was primary in the fibro-adenoma is difficult to determine since the whole breast was not available for study.

PERSISTENT ENTERIC MUCOSA AT THE UMBILICUS. ARTHUR W. WRIGHT.

A 13 year old white boy complained for one year of a small, moist, slightly painful, vascular tumor of the umbilicus. A physician removed the growth, which consisted of a globular mass of firm, skin-covered connective tissue, on the surface of which was the umbilical depression. In this depression there was a circular, congested, moist, yellowish-pink, slightly raised lesion which did not appear to be a tumor or an ulcer but which was distinctly abnormal. Microscopically, the mass proved to be evaginated intestinal mucous membrane which was congested and slightly inflamed. There was no evidence of malignant growth or ulceration. The lesion, clearly congenital, undoubtedly resulted from abnormal isolation of an island of enteric mucosa from the primitive vitelline duct which, during early embryonic life, extends out into the umbilical cord.

BUFFALO PATHOLOGICAL SOCIETY

Regular Meeting, Oct. 29, 1933

KORNEL TERPLAN, *President, in the Chair*

HISTOLOGIC DIAGNOSIS OF PREGNANCY FROM PLACENTAL FRAGMENTS. C. S. RYERSON and S. SANES.

This article will appear in the ARCHIVES.

CONGENITAL HEART DISEASE: INTERVENTRICULAR SEPTAL DEFECT, DEXTROPOSITION OF AORTA, AND DILATATION OF PULMONARY ARTERY. RAYMOND S. ROSEDALE.

The anomaly consisted of an unusual combination of dextroversio cordis, hypertrophy of the pulmonary artery, defect of the interventricular subaortic septum and dextroposition of a relatively small aorta. This was found in a 10 year old boy who since birth had been persistently troubled with dyspnea and cyanosis after exercise or emotional disturbance.

The foramen ovale was obliquely patent and measured 0.5 by 1 cm. The interventricular septal defect measured 2.5 by 3 cm. The diameters of the pulmonary artery and ascending aorta were as three to one. The large size of the closed ductus arteriosus suggested that it had been patent for some time after birth. There was hypertrophy of the musculature of both the left and right ventricles. The great branches of the aortic arch were anomalous, falling somewhat into the fifth class of anomalous great arteries as outlined by Piersol.

It was thought that the blood in the left ventricle had been partially shunted to the right ventricle. This was considered to have been due somewhat to a large muscle bundle that partially obstructed the aortic outlet. The fibrous portion of the aortic pulmonary septum was found to end blindly in this muscle bundle.

The normal equal division of the truncus and bulbus arteriosus had not taken place, for the remainder of the aorta which is not concerned with the septum trunci was of the same caliber as the ascending portion. The increase in size of the pulmonary artery and bulb was interpreted as hypertrophy and dilatation, postnatal in development.

It is suggested that the subaortic interventricular septal defect was probably due to the small size of the septum trunci and its failure to fuse with the posterior endocardial cushion.

The immediate cause of death was assumed to have been a general dilatation with coronary thrombosis; intimal thickening with plaques of adherent thrombi was noted in all the sections of the coronary and its branches.

A review of the literature revealed only four similar cases. The first was reported by Eisenmenger in 1897. The others were reported by M. E. Abbott and co-authors, who have referred to the combination of interventricular septal defect with dextroposition of the aorta and dilatation of the pulmonary artery as the "Eisenmenger complex."

ACUTE PNEUMOCOCCIC ENDOCARDITIS IN EARLY INFANCY. S. SANES and F. E. KENNY.

Of reported cases of acute bacterial endocarditis in infancy, only six can be accepted as adequately verified anatomically and bacteriologically (Blum, Dean, Dible, Terplan and associates, d'Evart, Brandes). In twenty-six other cases bacteriologic proof was not established; anatomic changes and occasionally embolic phenomena were noted, however.

CASE.—A white boy, aged 13 days, was admitted to the Children's Hospital because of cough, cyanosis and anorexia of three days' duration. The temperature was 103 F.; the pulse rate, 80. The nose was filled with purulent exudate; the

throat was red; there were diminished breath sounds and râles in both lungs. The heart was not enlarged; no thrill or murmur was elicited; the rate was regular, and the sounds were of good tone. The white blood cell count was 18,700, with 60 per cent polymorphonuclears and 40 per cent lymphocytes. On the ninth day a subcutaneous abscess appeared in the lumbar region; pneumococci were obtained in smears and cultures. Death occurred on the twenty-eighth day of life.

Autopsy, three hours after death, showed: confluent lobular pneumonia of the right upper and lower lobes, with small abscesses; a large abscess in the left psoas muscle extending into the subcutaneous tissue at the level of the third and fourth lumbar vertebrae; vegetative endocarditis of the ventricular surface of the tricuspid valve and of the posterior wall of the right ventricle beneath the attachment of the valve and of the conus pulmonaris; slight dilatation of the right ventricle, and congestion of the liver, spleen and kidneys. Smears and cultures from the vegetations and the lung revealed pneumococci.

Histologically, the right ventricle showed parietal endocarditis with fibrinous deposits containing many degenerated leukocytes and pneumococci. The tricuspid valve showed small vegetations directly beneath its attachment, with marked necrosis at its base and leukocytic infiltration. Pneumococci were found scattered throughout the vegetations as well as at the base of the valve. There were also pneumonic changes with fibrinous and leukocytic exudate and congestion of capillaries.

PRIMARY TUBERCULOUS FOCUS WITH EXTENSIVE CASEOUS PLEURITIS WITHOUT COMPLEX CHANGES IN THE REGIONAL LYMPH NODES. K. TERPLAN.

This case is presented because the anatomic findings showed an entirely unusual type of spread from a cheesy Ghon focus.

A white American woman, 23 years of age, was delivered spontaneously of a baby at full term, June 5, 1932. June 18, chills and fever made their appearance. These continued to occur for three days; then the patient was forced back to bed with headache, nausea and emesis. She was admitted to the hospital, June 27. The uterus was in position; there were no palpable evidences of extra-uterine infection. July 8, rigidity of the neck was evident. The patient died four days later.

The family history and past history could not be satisfactorily obtained.

A complete postmortem examination was made forty-eight hours after death. The body was emaciated, the skeletal system slender, the subcutaneous fat almost entirely absent.

The left lung was completely adherent to the parietal pleura, especially that on the diaphragm, mediastinum and pericardium. The right lung was free, with compensatory emphysema. The organs of the neck, thorax and abdomen were removed in toto; the thoracic duct was carefully dissected. In the removal of the left parietal pleura, a few small cheesy structures were revealed in the intercostal soft tissue above the anterior and lateral surfaces of the left lower lobe. In the left pleural cavity the mediastinal and diaphragmatic pleura was involved by marked cheesy infiltrations; the shape of the left lower lobe was changed, its base being distinctly contracted, measuring only 12 cm. in frontal diameter and 4.5 cm. in sagittal diameter. This was due to inversion of the basal margin, especially on the posterior side; the entire parietal pleura was thickened and pinkish gray and contained many tubercles; some of these invaded the diaphragm.

About 1 cm. above the base of the lung near the interlobar surface was a pea-sized caseous focus, from 0.5 to 0.6 cm. in diameter, immediately beneath the pleura. The pleura above this focus was firm, also inverted, and showed on cross-section caseous fibrosis. Caseous changes were also present on the external surface of the pericardium in connection with the caseous tuberculosis of the mediastinum on the left side. In the left upper and lower lobes were many pinhead-sized tubercles; those in the apex were somewhat larger and somewhat closer to each other.

There were no gross tuberculous lesions in the bronchomediastinal lymph nodes on the left side.

The lobes of the right lung showed numerous pinhead-sized tubercles. The lymph nodes on the right side were small and anthracotic. Only the lymph nodes in the left venous angle were grayish white, suggesting tuberculosis. All the lobes were dissected in very thin sheets. X-ray pictures were taken from the undissected lung as well as from the sheets of both lungs.

Older tuberculous lesions were not present in the intestine or in the mesenteric lymph nodes. Careful dissection of all organs, especially all lymph nodes, did not reveal a primary extrapulmonary tuberculous infection. A few of the left broncho-mediastinal nodes showed, however, microscopic tuberculosis with epithelioid cell tubercles, but without caseation. These changes were apparently secondary to the marked caseous pleuritis on the left side. The primary focus showed complete caseation in process of partial fibrous organization. Typical miliary tubercles were present in the leptomeninges, liver and spleen, and tuberculous infiltrates in the kidneys. The uterus was completely involuted and showed only small placental remnants without tuberculosis.

Anatomic dissection with thorough roentgen examination indicated that the caseous tuberculosis of the left pleural cavity had spread from a late primary caseous subpleural fibrous focus. The lymph nodes regional to the left lower lobe did not show caseous changes; in other words, no primary complex was formed. The tuberculous changes in the lymph nodes were microscopic and could be explained easily by the marked caseous pleuritis on the left side.

The entire picture can hardly be explained in any way other than by assuming an overwhelming primary infection, possibly acquired during pregnancy. Why the pleural cavity at once was infected to such a large extent as to produce diffuse caseous pleuritis, and why a lymphogenous spread to the lymph nodes regional to the focus did not occur, is difficult to state. It is known that the pleura above primary foci may be involved locally; very often even adhesions form. But such a pleural involvement remains restricted to the surface of the focus, while the lymph nodes draining the focus become involved very soon.

As the postmortem examination was complete and all organs were investigated for primary tuberculous lesions with negative results, it seems justified to consider the focus in the left lower lobe as the primary one in this case. Apparently, the overwhelming infection of the pleural cavity prevented the so-called complex changes in the lymph nodes regional to the focus.

Joint Meeting with the Buffalo Academy of Medicine, Nov. 29, 1933

MARGARET WARWICK, *President, in the Chair*

ANATOMIC STUDIES OF PRIMARY AND POSTPRIMARY PULMONARY TUBERCULOSIS IN WHITE CHILDREN AND ADULTS. K. TERPLAN.

Much of the present knowedge of primary human tuberculosis is based on careful gross pathologic work (Parrot, Kuss, E. Albrecht, Ghon, H. Albrecht and Opie). In progressive pulmonary tuberculosis in adults, the anatomic picture tends to be complicated; often it seems difficult to trace the changes back to the first lesion. It is generally believed that the disease usually develops in connection with a so-called reinfection. There is some controversy as to the manner of this reinfection; that is, as to whether it is a reinfection from outside the body while the first lesions are healing or are still active, or whether it is a so-called endogenous reinfection or exacerbation originating in the primary focal lesion or in the regional lymph nodes. This question ought to be studied individually in each case. The structural lesions in the lungs of adults who have died from progressive chronic pulmonary tuberculosis are often too extensive to serve properly as material for pathogenic studies. On the other hand, in examining cases in which death was not due to tuberculosis, many pathologists, satisfied with finding one typical calcified tuberculous complex, have assumed that this complex was the only lesion.The x-ray

picture has helped in detecting calcified foci, and one usually has taken for granted that round shadows of calcification represented tuberculous foci.

As far as early changes, especially in so-called reinfection, are concerned, incidental findings may sometimes be of great value. Because the early lesions are usually less extensive it is easier to discover the paths along which they developed.

The study of the pathogenesis of tuberculosis cannot be thorough enough. It not only has to include minute dissection and taking of roentgenograms, but also a complete histologic examination of all focal lesions found by roentgen examination and dissection.

In the present study I have attempted merely to register and analyze all findings of a tuberculous nature without trying to correlate them with present theories derived from experiments on animals which are so readily used to explain in general terms of immunity the individually different lesions of human tuberculosis.

From the data contributed in the past fifteen years a few more or less dogmatic statements have been made. For example: All children in cities acquire their first tuberculous lesion before they reach adult life. Tuberculosis in adults acts altogether differently from that in children; it usually starts in the apex; it is acquired from without; the tributary lymph nodes are not involved. When miliary tuberculosis occurs in adults it is only because they have escaped childhood infection. Small foci give scant resistance; marked focal lesions give marked resistance.

It is customary to group all tuberculous lesions into childhood and adult types. This predicates that tuberculosis is always first acquired in childhood, and that tuberculosis in adults usually does not show the striking lesions of first infection, with a primary focus and involvement of regional lymph nodes. I prefer the terms "primary tuberculosis" and "postprimary tuberculosis." The latter is wide enough to cover the different ways of so-called reinfection.

It is stated that adults react like reinfected animals in the allergic stage. Still one does not know why these reactions in man vary so markedly, sometimes remaining localized in fulfilment of the experimental postulates, and sometimes spreading not only along the bronchi, but also to lymph nodes, like a primary lesion, and through blood vessels. Medical examination does not prove that with a similar exposure children of the same family are apt to acquire progressive tuberculosis or so-called reinfection. Tuberculosis in man appears much more complicated in its origin and course than that produced by well graded experiments on animals. Spontaneous tuberculosis in animals comes surely closer to being the counterpart of human tuberculosis.

Modern advances especially in the treatment and prevention of tuberculosis have a distinct bearing on the apparently decreasing incidence of tuberculous lesions in childhood in the white race. Although the total number of children examined in this study is small (271 from 1 month to 6 years of age, and 50 from 7 to 18 years of age) the figures show that primary tuberculosis does not always occur during childhood, but apparently occurs rather in the early years of adult life. In general, the figures indicating the incidence of focal tuberculous lesions up to the eighteenth year vary between 20 and 25 per cent. They are apparently in line with the figures on positive reactions to tuberculin tests as published by pediatricians in Massachusetts, Minnesota, Wisconsin and Cattaraugus County, New York, and from different schools in Buffalo. The number of children giving positive reactions gives only the lowest number of the once infected children, as it is likely (proved by my experience in two instances) that with anatomic healing of small focal lesions, the reaction to tuberculin becomes negative again. With exception of Opie's work in St. Louis and Philadelphia, no systematic postmortem examinations have been made in this country with a view to studying the incidence of primary focal lesions in children and young adults. Apparently it has been taken for granted from the figures of Kuss, Ghon, Aschoff and Opie that primary foci are acquired by all children before they reach adult life.

The total number of persons between the twentieth and fortieth years of life examined postmortem for this study is again small (total number 28) and cannot be used as a basis for statistical study. However, the majority of them (from

67 to 75 per cent) showed lesions of primary tuberculosis. After the fortieth year of life the person who revealed no such lesion was exceptional. I encountered primary focal lesions with caseous and caseofibrous complexes in about eight persons between the fourth and the eighth decade of life. These lesions acted similarly to first lesions seen in childhood. The development of progressive tuberculosis is not, except possibly in infancy and early childhood, predominantly determined by the age of the patient. In the study of focal lesions histologic examination of older calcified and ossified foci affords no means of distinguishing absolutely between primary and postprimary tuberculous infection. The older the lesions the more exactly do they resemble each other, each exhibiting remnants of so-called caseous pneumonia which can be demonstrated in a calcified stage by stains for elastic tissue. The mesenchymal reaction surrounding localized lesions may or may not differ in primary and postprimary foci. Puhl's criteria can be used only in the small number of cases in which the postprimary lesions are progressing or are in the early stages of healing. Contrary to commonly accepted teaching, the findings which I report indicate that postprimary infection may produce complex changes identical with those seen in primary tuberculosis. Progressive postprimary lesions often tend to be accompanied by changes in regional lymph nodes. These changes are in general microscopic. In older persons, however, they may be just as active and extensive as are those in many cases of primary infection. Some instances of this active, extensive development may represent the so-called lymphendogenous reinfection.

The presence of ossified healed lesions on one side and of older ossified complexes on the other may be explained by a development of multiple primary lesions simultaneously with a one-sided spread, by a reinfection that occurred many years previously, or by a secondary bronchiogenic spread from the first lesion while it was still active. The last possibility appears to be substantiated in cases in which one finds, closely surrounding an old primary lesion, fibrous tubercles and recent caseous bronchiogenic spread.

In proved cases of reinfection apparently exogenous in origin, the site of lesion is most often in the upper half of an upper lobe, from 2 to 4 fingerbreadths below the apex. The summit or apex is only occasionally primarily involved, and the lower part of the upper lobe or the lower lobe, less frequently. With this distribution of secondary lesions, the clinical designation "infraclavicular tuberculous infiltrate" becomes more satisfactory than "tuberculous apical infiltrate."

To summarize: From the postmortem material examined in the last three years at the Buffalo General Hospital and the Children's Hospital it seems that the first tuberculous infection commonly takes place in the first three decades of life, especially from the age of puberty to that of from 20 to 30 years, and only occasionally later. Postprimary lesions may produce so-called complex changes in lymph nodes similar to those of primary infection.

How far multiple foci prevent lymphatic spread is a question that cannot be appropriately or satisfactorily discussed from the point of view of these studies dealing, as they do, chiefly with older or healed lesions. Although the law of Parrot still stands well founded as a general working principle, it must not be considered an absolute, inflexible dogma. As I have shown, primary focal lesions may remain entirely restricted in the lung, without changes in the regional lymph nodes. The incidence of focal lesions without complex changes cannot be accurately expressed, because many such lesions are probably overlooked unless a thorough search is made for them.

In a certain number of cases in adults and even in children marked progressive involvement of the lungs is not accompanied by acute miliary tuberculosis. A subacute hematogenous spread occurs. Tuberculous meningitis, however, may constitute the dénouement of the disease.

The practicability of adhering to a rigid classification of tuberculosis based on experimental findings becomes, in the light of the multiform lesions and varied courses in individual human beings, an open question.

Book Reviews

De Venarum Ostiolis 1603 of Hieronymus Fabricius of Aquapendente (1533?-1619). A facsimile edition, with introduction, translation and notes, by Kenneth J. Franklin, D.M., Tutor and Lecturer in Physiology of Oriel College and University, Demonstrator of Pharmacology, Oxford. Price, $3. Pp. 104, with 7 figures and 8 plates. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

This book is published by the aid of a grant from the History of Science Society, which has received an appropriation from the Carnegie Corporation of New York to enable it "to publish, or assist in publishing, important contributions to knowledge." In addition to the facsimile reproduction and translation of "De Venarum Ostiolis," published in 1603, the book contains a biographic note on Fabricius, a section on the early history of work on the venous valves, a short account of the anatomic theater at Padua and a bibliographic note, for which the dedicatee, Prof. J. F. Fulton, is chiefly responsible concerning the first edition. Besides reproductions of the original plates and the frontispiece showing Fabricius as portrayed in 1630, the illustrations include the following: the statue of Fabricius in Aquapendente; the earliest drawings of a venous valve (Alberti, 1585), the theater of Fabricius, with the plan and elevation, and a reproduction of a general title page of his "Opera anatomica," published in 1625. The book is printed with special care on Patten rag paper. The publisher is worthy of commendation for publishing at this time a book of historic interest in such attractive form.

In his preface Dr. Franklin points out that "the discovery of the circulation by William Harvey was in large measure due to his correct estimate of the function of the venous valves, and about these he had heard while studying under Hieronymous Fabricius at Padua from 1600 to 1602." He then quotes the following account by Robert Boyle of a conversation with Harvey: "And I remember that when I asked our famous Harvey, in the only Discourse I had with him (which was but a while before he dyed), What were the things that induc'd him to think of a Circulation of the Blood? He answer'd me, that when he took notice that the Valves in the Veins of so many several Parts of the body, were so Plac'd that they gave free passage to the Blood Towards the Heart, but oppos'd the passage of the Venal Blood the Contrary way: He was invited to imagine, that so Provident a Cause as Nature had not so Plac'd so many Valves without Design: and no Design seem'd more probable, than That, since the Blood could not well, because of the interposing Valves, be Sent by the Veins to the Limbs; it should be Sent through the Arteries, and Return through the Veins, whose Valves did not oppose its course that way." Hence one has in readily accessible and appropriate form the original and the translation of a book of fundamental importance in the history of the discovery of the circulation of the blood.

Metabolic Diseases and Their Treatment. By Dr. Erich Grafe, Professor of Medicine of the Clinic of Medicine and Neurology at the University of Würzburg, Germany. Translated by Margaret Galt Boise under the supervision of Eugene F. DuBois, M.D., Medical Director, Russell Sage Institute of Pathology, and Professor of Medicine, Cornell University Medical College, New York, and Henry B. Richardson, M.D., Associate Professor of Medicine, Cornell University Medical College, New York. Cloth. Price, $6.50, net. Pp. 551, with 37 engravings. Philadelphia: Lea & Febiger, 1933.

The German edition of Professor Grafe's book was published in 1931. It was soon recognized as a comprehensive and conservative presentation of the modern German views on the diseases of metabolism. Grafe is particularly well fitted to

discuss the scientific and practical aspects of this subject. Trained in the school of Rubner, he has made original and important contributions in the fields of respiratory and intermediary metabolism. At the same time he has been advancing in clinical medicine and has attained one of the most important professorships in Germany. He is one of the few leaders in his country who have kept in touch with the American literature. His book covered the subject so well and filled such a large gap in the modern literature that Lea & Febiger arranged for a translation, with extensive revisions by Grafe which brought the material up to 1933.

The translation has evidently been made with considerable care and seems to preserve as closely as possible the original ideas of the author. The text still contains references to many German proprietary medicines with which physicians in this country are unfamiliar, but apparently the author has cut out about half of those which appeared in the original edition. One must remember that there is no Council on Pharmacy and Chemistry in Germany and that thousands of proprietary medicines are used throughout the Continent without adequate supervision. The Continental tendency toward inaccuracies in references was evident in the original; these inaccuracies have been partly corrected though not entirely eliminated in the translation. There are some typographical errors; for example, in table 22, page 193, 1.0 salyrgan appears as 1 mg. salyrgan. Both are wrong; the dose evidently should have been 1 cc. of a 10 per cent solution of salyrgan.

On the whole, the book is well written, and makes easy reading for one who is interested in the diseases of metabolism. For the teacher and research worker it is a valuable source book. The chapters on obesity and malnutrition are particularly good. There is an excellent discussion of the theories and treatment of gout by an observer who has had unusual opportunities for studying the disease at first hand. The subject of diabetes is well handled, and there are brief but adequate chapters on the rarer diseases of metabolism and the vitamin deficiencies. There are no special sections devoted to basal metabolism or to diseases of the thyroid gland, but references to these are scattered throughout the volume. In general, the field of metabolism is covered in a critical and conservative manner.

Books Received

BAC. PARATYPHOSUS B BELYST VED UNDERSØKELSER OVER PARATYFUS-B-STAMMER FRA VEST-NORGE OG OVER SYGDOMMENS OPTREDEN SAMMESTEDS. T. M. Vogelsang. Pp. 235, with 9 figures. Bergen: J. W. Edes Boktrykkeri A/S, 1933.

This monograph is based on the study of strains of paratyphoid B obtained from patients with paratyphoid fever in the western part of Norway. Paratyphoid bacillus B is different from the bacteria of food poisoning and causes a typhoid-like disease, paratyphoid B fever. This disease is spread from person to person directly or indirectly and appears to be quite as specific as typhoid fever. Other sources of infection have not been demonstrated definitively.

HOUSING CONDITIONS AND RESPIRATORY DISEASE: MORBIDITY IN A POOR-CLASS QUARTER AND IN A REHOUSING AREA IN GLASGOW. C. M. Smith. Medical Research Council, Special Report Series, No. 192. Price, 9d. Pp. 36. London: His Majesty's Stationery Office, 1934.

AIDS TO PATHOLOGICAL TECHNIQUE. David H. Haler, M.B., B.S. (Hons.) Lond., Pathologist, Infants Hospital, Battersea General Hospital, etc. Price, $1.50. Pp. 187. Baltimore: William Wood & Company, 1933.

This booklet does not deal with the examination of tissues. The methods described are mainly bacteriologic, hematologic, cytologic and biochemical—"one example of each method found most valuable."

DIE SPEZIFIZITÄT DER SEROLOGISCHEN REAKTIONEN. K. Landsteiner, the Rockefeller Institute for Medical Research, New York. Price, 8.80 marks. Pp. 123, with 22 tables and 1 illustration. Berlin: Julius Springer, 1933.

DISSECTING ANEURYSMS. T. Shennan. Medical Research Council, Special Report Series, No. 193. Price, 2s. 6d. Pp. 138, with 13 figures. London: His Majesty's Stationery Office, 1934.